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Application of the Moore Rearrangement to the Synthesis of 1,4-Dioxygenated Xanthones and Efforts Toward the Total Synthesis of Lundurine B

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Application of the Moore Rearrangement to the Synthesis of 1,4-Dioxygenated Xanthones and Efforts Toward the Total Synthesis of Lundurine B

by

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Dedication

For my parents: Mark and Janice. Thank you.

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Application of the Moore Rearrangement to the Synthesis of 1,4-Dioxygenated Xanthones and Efforts Toward the Total Synthesis of Lundurine B

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The University of Texas at Austin, 2012

Supervisor: Stephen F. Martin

A novel application of the Moore rearrangement was successfully developed and applied to the synthesis of 1,4-dioxygenated xanthones that would have been difficult to obtain otherwise. The 1,4-dioxygenated xanthone moiety is found in several naturally occurring, biologically active compounds. Several methods by which to obtain the 1,4-dioxygenated xanthone core have been reported; however, high step counts, low yields, and harsh reaction conditions preclude the use of these methods to complex xanthone natural products. Using the Moore rearrangement as a key step in the synthetic sequence has allowed us to prepare several xanthone natural products quickly and more efficiently than what is possible with the prior art.

Using the Martin group's prior experience with the application of ring closing metathesis (RCM) to the field of alkaloid natural product synthesis, the preparation of lundurine B was undertaken. Key features of the proposed synthesis to lundurine B include the formation of a cyclopropane ring by the formation pyrazoline intermediate *via* [3+2] dipolar cycloaddition followed by dinitrogen extrusion. A second key step in the

proposed sequence to lundurine B is a double RCM to form a five- and eight-membered ring in a single operation. While double RCM strategies have been applied to several elegant natural product syntheses, the formation of a five- and eight-membered ring in a single sequence has not been reported. Should the double RCM strategy prove successful for lundurine B, the conditions could in principle be applied to other structurally related natural products.

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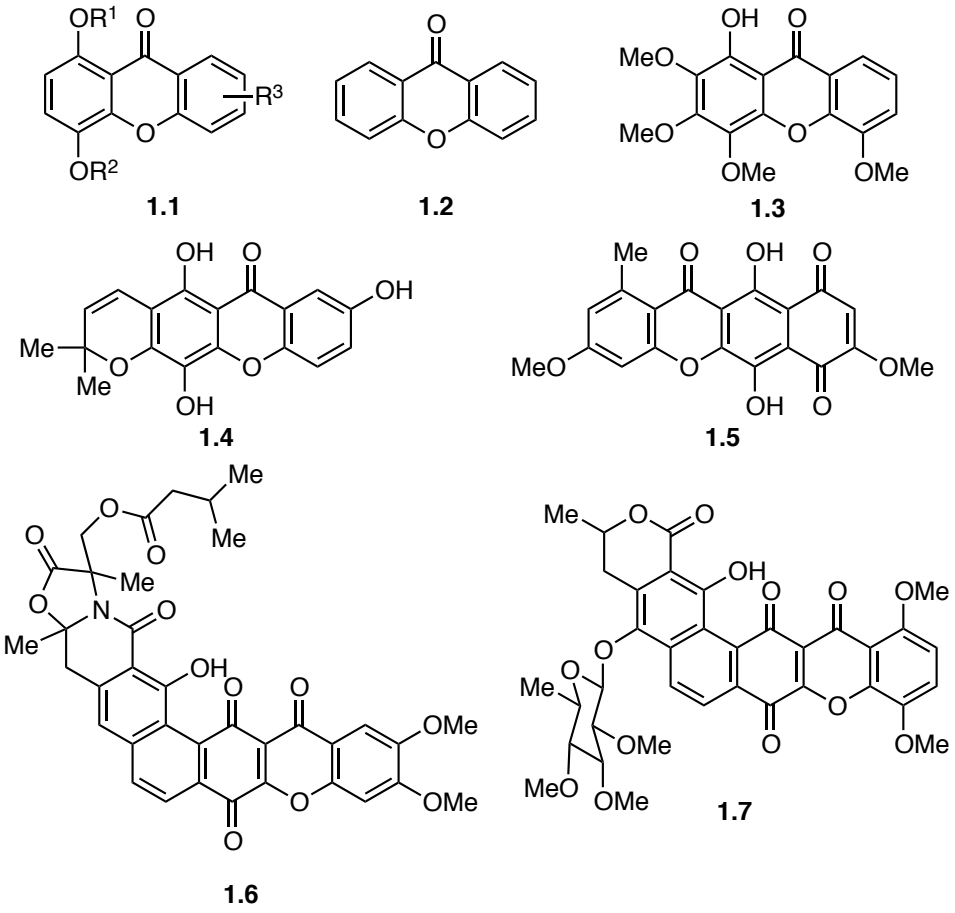
Chapter 1: 1,4-Dioxygenated Xanthones and Related Natural Products

1.1 The 1,4-Dioxygenated Xanthone

The 1,4-dioxygenated xanthone core **1.1** is a subunit in an important class of natural products within the xanthone family (Figure 1.1).[1] Currently, well over 1000 naturally occurring xanthones with core **1.2** have been isolated.[1-3] Many of these xanthones have interesting architectures that inspire synthetic endeavors, whereas others possess biological activity that is equal to if not more appealing than the structures themselves. The simple tricyclic xanthone **1.3** is reported to inhibit the formation of osteoclasts *in vitro*,[4] while the more complex tetracyclic xanthone atroviridin (**1.4**) is commonly used in traditional medicine as a remedy for earaches.[5] Atrovoridin has been prepared on two separate occasions by Theodorakis[6] and Suzuki.[7] One of the more well-known xanthones isolated is bikaverin (**1.5**).[8,9] This tetracyclic natural product is reported to have outstanding antifungal properties as well as cytotoxicity activity.[8] Compound **1.5** contains a quinone moiety as well as the 1,4-dioxygenated xanthone core and has inspired synthetic endeavors ever since isolation. Citreamicin α (**1.6**) is a representative member of a class of quinone-xanthones.[10,11] The angularly fused heptacyclic quinone-xanthone, as well as other members of the citreamicin family, has *in vitro* activity against lung and colon carcinoma with IC_{50} of 4 nM.[10] IB-00208 (**1.7**) is another angularly fused xanthone with impressive biological activity,[12] having a minimum inhibitory concentration (MIC) of 1 nM against numerous human cancer cell lines. It is also active against Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* with an IC_{50} of 1.4 nM.[13] To date, there have been no total syntheses of **1.6** or **1.7**; however, the preparation of both xanthones is ongoing within the Martin group.

Figure 1.1 1,4-dioxygenated xanthones and related natural products



Numerous of approaches have been developed for the preparation of xanthones with a general structure such as **1.2**, and in fact reviews just on the synthesis of xanthones have been published.[3,14,15] Many approaches provide access to substitution patterns that are limited to a single xanthone natural product or a family of structurally similar xanthones. Surprisingly, there is a paucity of general methods currently available for the preparation of 1,4-dioxygenated xanthones, especially in the context of natural products. Many approaches to the xanthone core **1.2** are not readily applicable to 1,4-dioxygenated xanthones due to an unnecessarily high step count, tedious preparation of the starting

materials, and low yielding sequences. The known methods that have led to 1,4-dioxygenated xanthones will be discussed in the following sections.

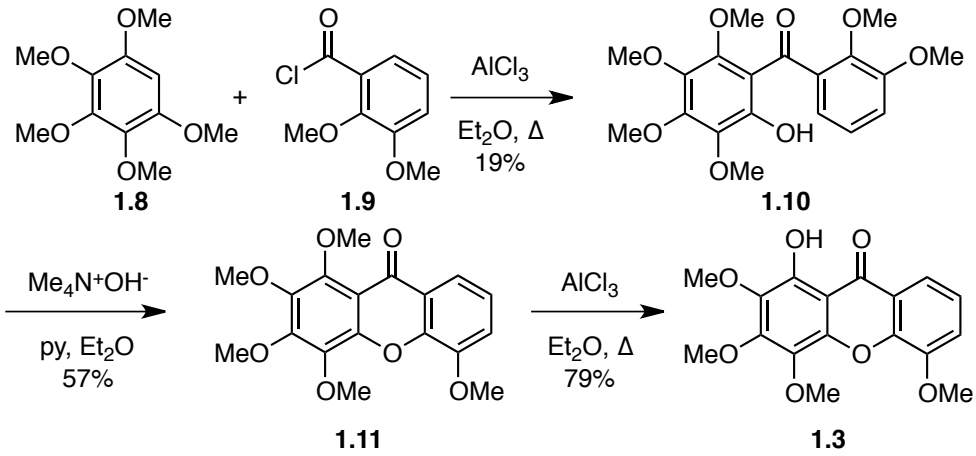
1.2 The Synthesis of 1,4-Dioxygenated Xanthones

1.2.1 Benzophenone intermediate

The most common method to prepare 1,4-dioxygenated xanthones is through the formation of a benzophenone intermediate using a Friedel-Crafts reaction (Scheme 1.1). Historically, an acid chloride and an electron rich aromatic ring are coupled in the presence of a strong Lewis acid to form a benzophenone. Stout and Balkenhol were the first to apply this reaction to the synthesis of 1,4-dioxygenated xanthone natural products.[16] In their approach, condensation of 1,2,3,4,5-pentamethoxybenzene (**1.8**), which is available in six steps from commercial material,[17] with acid chloride **1.9** provided the desired benzophenone **1.10** in 19% yield. The phenolic oxygen atom *ortho* to the carbonyl group was also unmasked in the same reaction due to the excess Lewis acid present. The deprotection of the phenol was fortuitous because the benzophenone **1.11** then underwent nucleophilic aromatic substitution under basic conditions to give the desired xanthone **1.12** in 57% yield. The final reaction, a second demethylation *ortho* to the carbonyl group, took place in 79% yield to provide **1.3** in ten steps and 2.1% overall yield. This method retains popularity in the context of total synthesis because the starting materials are readily available, the reactions are relatively easy to perform, and purification is often done by recrystallization. However, this method has significant drawbacks in that the reaction conditions commonly used to deprotect the phenol require harsh reaction conditions and can call for strong Lewis acids such as BBr_3. Products suffering from over-demethylation are commonly isolated along with the desired product, and acid sensitive or Lewis basic functional groups may not survive the strongly Lewis

acidic conditions. Furthermore, if an unsymmetrical nucleophile is used during the acylation step, there is a chance to form regioisomeric compounds. The Friedel-Crafts approach, although useful, is best suited for the preparation of relatively simple xanthones.

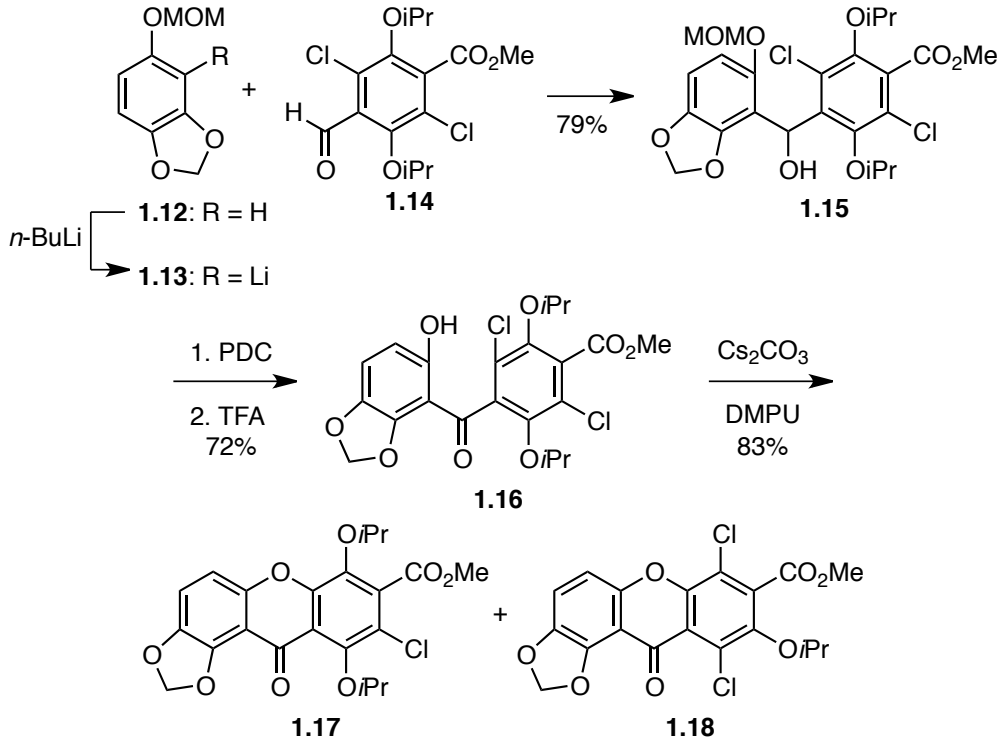
Scheme 1.1 Friedel-Crafts approach to 1,4-dioxygenated xanthones



Suzuki has put forth a convergent, multi-step method to access 1,4-dioxygenated xanthones *via* a benzophenone intermediate (Scheme 1.2).[18] In the first step of the sequence, an aromatic nucleophile **1.13**, formed from the directed metalation of **1.12**, was reacted with an aryl aldehyde **1.14** to give benzylic alcohol **1.15** in 79% yield. The alcohol was then oxidized to the benzophenone with PDC, and the phenol was deprotected with TFA to give **1.16** in 72% overall yield. The benzophenone **1.16** was then treated with Cs_2CO_3, which then underwent S_nAr with loss of a chloride ion to give the desired xanthone **1.17** in 83% yield. The strongly basic requirements of Suzuki's method preclude the use of base-sensitive substrates in this sequence. Another significant drawback to this method is the formation of regioisomeric products. Suzuki also reported that the xanthone **1.17** was contaminated with **1.18** in varying amounts.

The formation of **1.18** presumably arises from the S_nAr of the regioisomeric position, with isopropoxide acting as the leaving group.

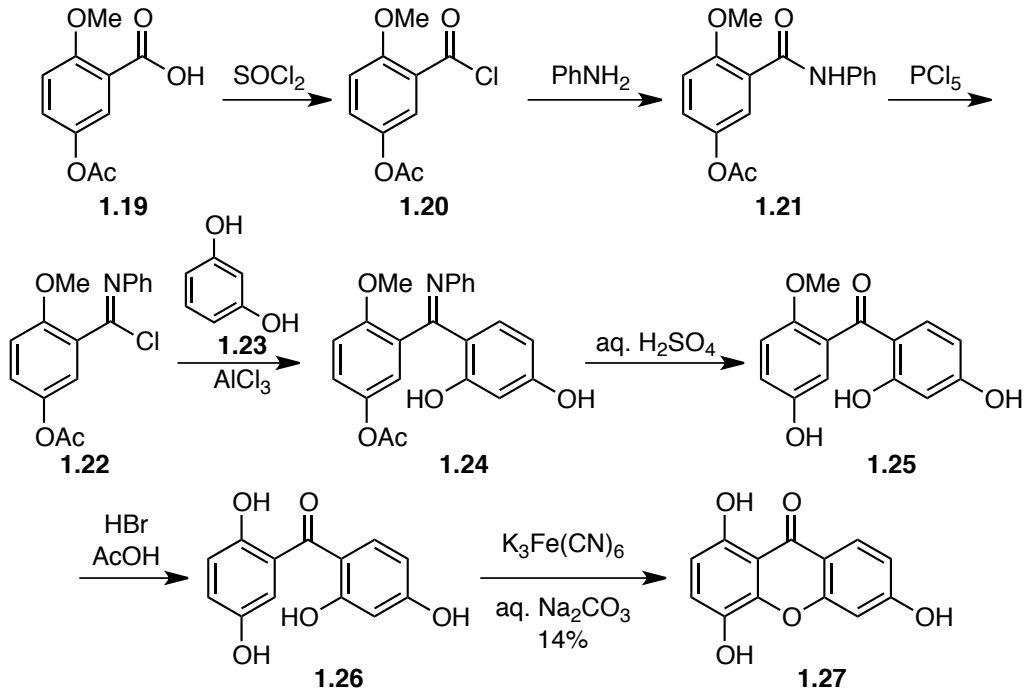
Scheme 1.2 Suzuki's synthesis of 1,4-dioxygenated xanthones



Whalley and coworkers described a biogenetic type of cyclization to give the 1,4-dioxygenated xanthone core *via* a benzophenone intermediate (Scheme 1.3).[19] The benzoic acid of **1.19** was converted to the acid chloride **1.20** and immediately treated with aniline to give the anilide **1.21**. Dehydration of **1.21** with PCl_5 delivered the chloroimine **1.22**, which upon mixing with resorcinol (**1.23**) in the presence of $AlCl_3$ furnished the Friedel-Crafts product **1.24**. The benzophenone imine **1.24** was then hydrolyzed under acidic conditions to the benzophenone **1.25**. The phenolic oxygen atoms of **1.25** were unmasked under strongly acidic conditions to give the tetraphenol benzophenone **1.26**. After some experimentation, the authors found that reaction of **1.26** with $K_3Fe(CN)_6$

under basic conditions delivered the 1,4-dioxygenated xanthone **1.27** in 14% yield. While this was an important contribution to the field of 1,4-dioxygenated xanthones, the high step count to the benzophenone as well as the low yielding oxidation and cyclization sequence prevent the application of this methodology to the synthesis of highly complex natural products. A similar approach to a benzophenone imine core **1.24** on route to 1,4-dioxygenated xanthones was reported by Townsend and coworkers.[20]

Scheme 1.3 Whalley's biogenetic synthesis of xanthones

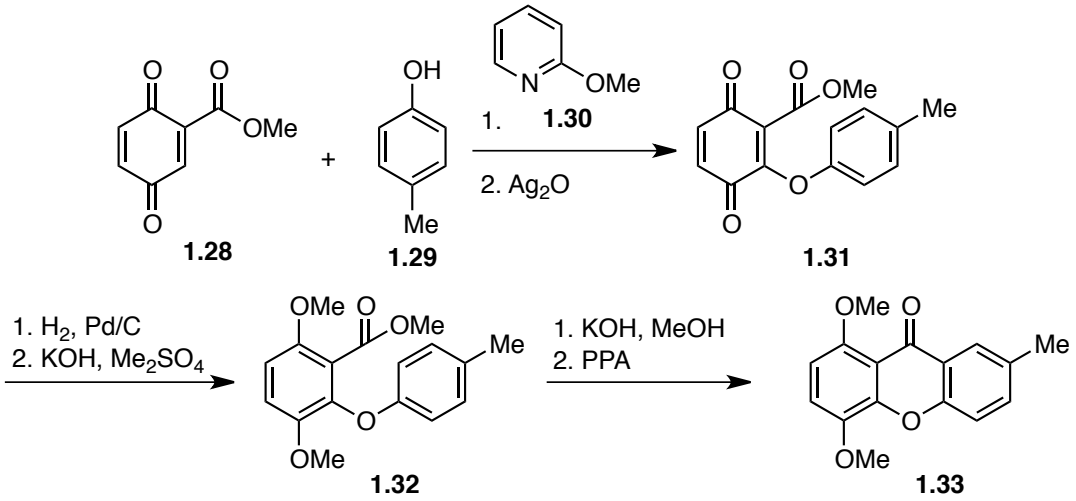


A significant problem with using benzophenone intermediates concerns the low yielding sequences and high step counts. Deprotection of methoxy groups at positions *ortho* to carbonyls is known,[21] but the harsh reaction conditions often lead to undesired side reactions. These problems were addressed by using a quinone as an electrophile.

1.2.2 Quinones as electrophiles

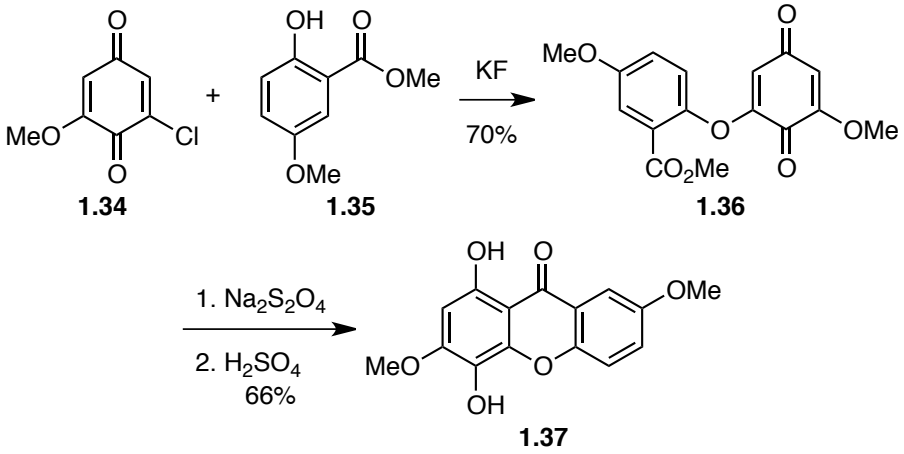
When a quinone is used as an electrophile, there is no need to employ harsh Lewis acids to unmask a phenol for cyclization. Müller published one of the first direct routes to a 1,4-dioxygenated xanthone using a quinone as the precursor to the hydroquinone moiety (Scheme 1.4).[22] In the event, reaction of quinone methyl ester **1.28** with *p*-cresol (**1.29**) in the presence of 2-methoxypyiridine (**1.30**) delivered an intermediate hydroquinone. The hydroquinone was then oxidized to the quinone **1.31** by the action of Ag_2O. The choice of base was extremely important to the success of this reaction, and it was found that **1.30** was the only reagent that gave the desired product. Side products were formed when reagents other than **1.30** were used. Unfortunately, yields were not reported for the reaction sequence. Aryl ether **1.31** was reduced to the hydroquinone with Pd/C, and the phenols were methylated with Me_2SO_4 to provide **1.32**. The methyl ester of **1.32** was saponified, and the acid was then heated in polyphosphoric acid (PPA) to deliver the xanthone **1.33**. While this was a clever strategy to prepare 1,4-dioxygenated xanthones, this was the only example that Müller reported. Several years later, Wagner and coworkers applied this methodology in their syntheses of glycosylated xanthones.[23] While the issue of low yielding sequences cannot be assessed since yields were not reported for the reaction in Scheme 1.4, the overall sequence appears to be more tolerant to Lewis acid sensitive functional groups. Unfortunately, the final cyclization was performed in neat PPA, which would not be compatible with acid sensitive functional groups on the molecule.

Scheme 1.4 The synthesis to 1,4-dioxygenated xanthones using quinones



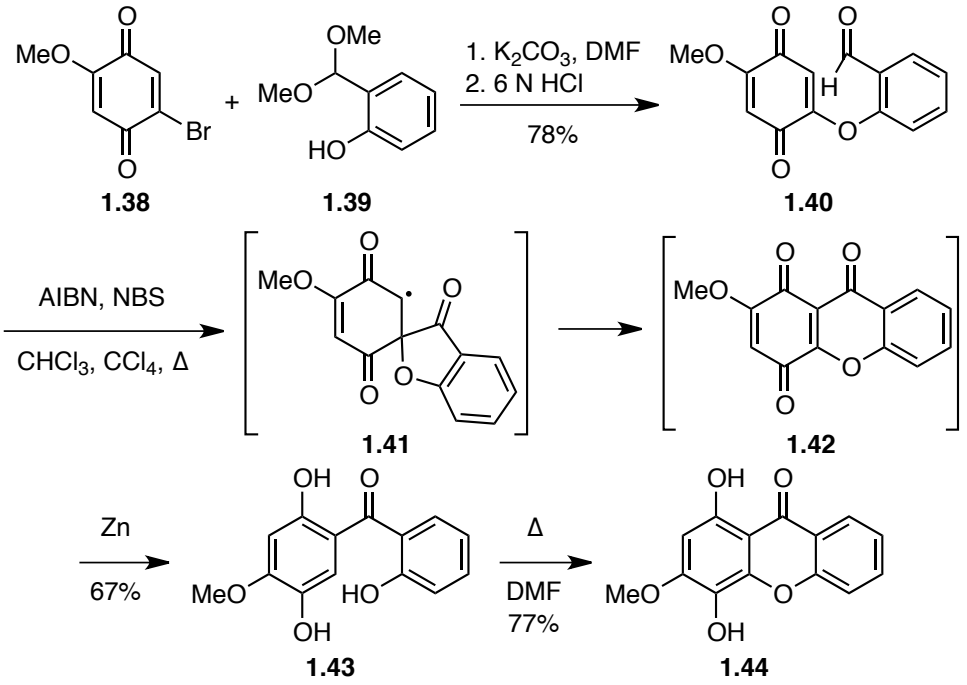
A strategy to address the high step count that plagued the approaches involving benzophenone intermediates was first reported by Brassard and coworkers (Scheme 1.5).[24] Treating a mixture of chloroquinone **1.34**[25] and methyl salicylate **1.35** with KF as base provided aryl ether **1.36** in 70% yield. The quinone was reduced under standard conditions and cyclization occurred under strongly acidic conditions to provide the xanthone **1.37** in 66% overall yield. This method does provide the 1,4-dioxygenated xanthone in fewer operations than the other methods discussed previously. Brassard elegantly demonstrated that by using a chloroquinone several steps could be saved. Unfortunately, the biggest shortcoming to this method is the preparation of the starting chloroquinone. Low yields and byproducts are commonly observed for the preparation of **1.34** as well as other chloroquinones.[25]

Scheme 1.5 Chloroquinones in the synthesis of 1,4-dioxygenated xanthones



Kraus and coworkers recently disclosed a method to 1,4-dioxygenated xanthones using quinones as an electrophile (Scheme 1.6).[26] The synthesis began with the reaction of phenol **1.39** with the brominated quinone **1.38**[27] under basic conditions. The resulting acetal was then deprotected to provide the aryl aldehyde **1.40** in 78% overall yield. In their key step, reaction of **1.40** with NBS in the presence of AIBN generated an acyl radical that cyclized *via* a 5-*exo*-trig fashion to the proposed spirocyclic radical intermediate **1.41**. The spirocycle **1.41** then rearranged to the quinone xanthone **1.42**, which was subsequently reduced with excess Zn in AcOH to provide the benzophenone **1.43** in 67% yield. Heating **1.43** in DMF under reflux afforded the 1,4-dioxygenated xanthone **1.44** in 77% yield presumably after undergoing oxidation to the quinone *in situ*. This methodology does provide access to the target xanthone. However, the overall yield for each of the reported examples is less than 40%, the cyclization to the xanthone requires heating to 180 ˚C in DMF, and the preparation of the benzophenone **1.43** is probably better suited for Friedel-Craft chemistry rather than this stepwise approach.

Scheme 1.6 Kraus' acyl radical approach to 1,4-dioxygenated xanthones

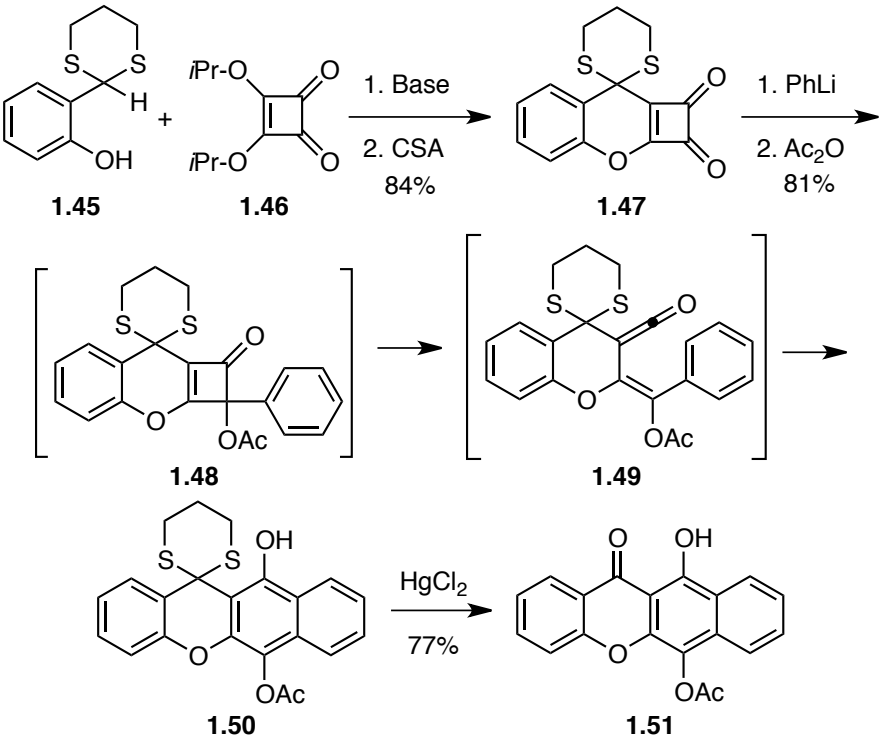


1.2.3 Benzannulation approach

Liebeskind applied his well-known benzannulation chemistry to the preparation of 1,4-dioxygenated xanthones (Scheme 1.7).[28,29] In this sequence, the dianion of a dithiane-protected salicylaldehyde **1.45** was allowed to react with diisopropoxysquarate (**1.46**)[30] to provide the tetracycle **1.47** after acid catalyzed hydrolysis. Reaction of tetracycle **1.47** with phenyllithium proceeded with complete regioselectivity[31] at the ketone carbonyl group, and the resulting alkoxide was trapped with acetic anhydride to provide intermediate **1.48**. Under the reaction conditions, a facile 4π electrocyclic ring opening reaction occurred to give the intermediate ketene **1.49**, which immediately underwent a 6π electrocyclic benzannulation to give **1.50** in 81% yield. The dithiane-protecting group was removed, and the xanthone **1.51** was isolated in 77% yield. This method provides much more flexibility than the preceding methodologies because the

nucleophiles may vary from aromatic to heteroaromatic partners. Yields of the addition and benzannulation sequences are between 40-90%. One downside to this method is that only symmetrical aromatic nucleophiles can be used because of the likelihood to form regioisomers during the benzannulation step.

Scheme 1.7 Liebeskind's annulation reaction to 1,4-dioxygenated xanthones

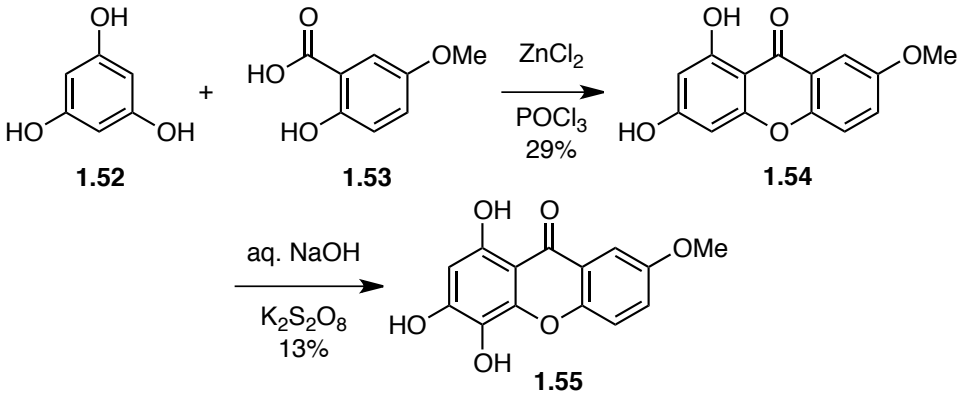


1.2.4 The Elbs oxidation

The application of the Elbs oxidation to the xanthone family was first reported by Jain and coworkers (Scheme 1.8).[32] Xanthone **1.54** was prepared in 29% yield by the reaction of phloroglucinol (**1.52**) with salicylic acid **1.53** employing the method of Grover, Shah and Shah.[33] Utilizing the traditional Elbs oxidation conditions, the authors exposed **1.54** to aqueous persulphate under basic conditions to provide the desired 1,4-dihydroxyxanthone **1.55** in 13% yield. This method provides a quick preparation of 1,4-

dioxygenated xanthones because the starting materials are typically readily available. The largest disadvantage to this method concerns the yield of the oxidation. Other reported examples of an Elbs oxidation to obtain 1,4-dioxygenated xanthones commonly report below 30%.

Scheme 1.8 The Elbs oxidation as a key step to prepare xanthones

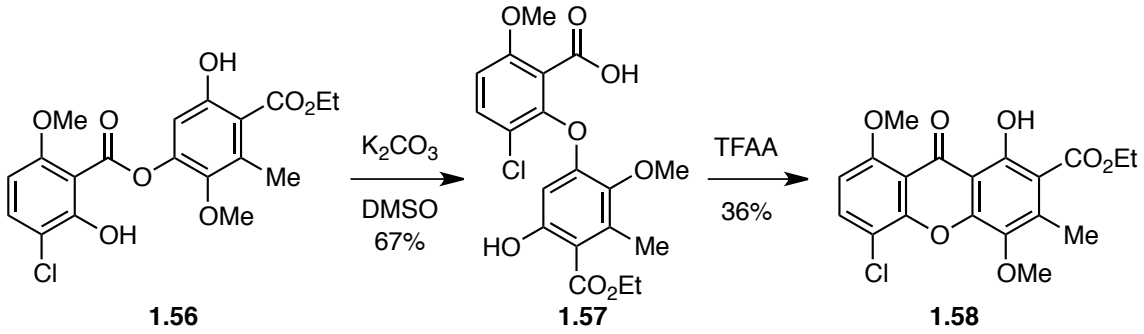


1.52 **1.53** **1.54** **1.55**

1.2.5 The Smiles rearrangement

A highly functionalized 1,4-dioxygenated xanthone was synthesized by incorporating a Smiles rearrangement in the synthetic sequence (Scheme 1.9).[34] In the event, diphenyl ester **1.56** was exposed to basic conditions to produce the diphenyl ether **1.57** in 67% yield. The mixed anhydride of **1.57** was then generated with TFAA, at which time the electrophilic aromatic substitution reaction took place to give the xanthone **1.58** in 36% yield. This method is very powerful in that electron withdrawing groups and halogens are both tolerated in the sequence. One caveat is that the location of the ester, which is vital to the Smiles rearrangement, must be *para* to the biaryl ether linking oxygen. Without this particular substitution, the Smiles rearrangement would not work.

Scheme 1.9 Use of a Smiles rearrangement to access 1,4-dioxygenated xanthones

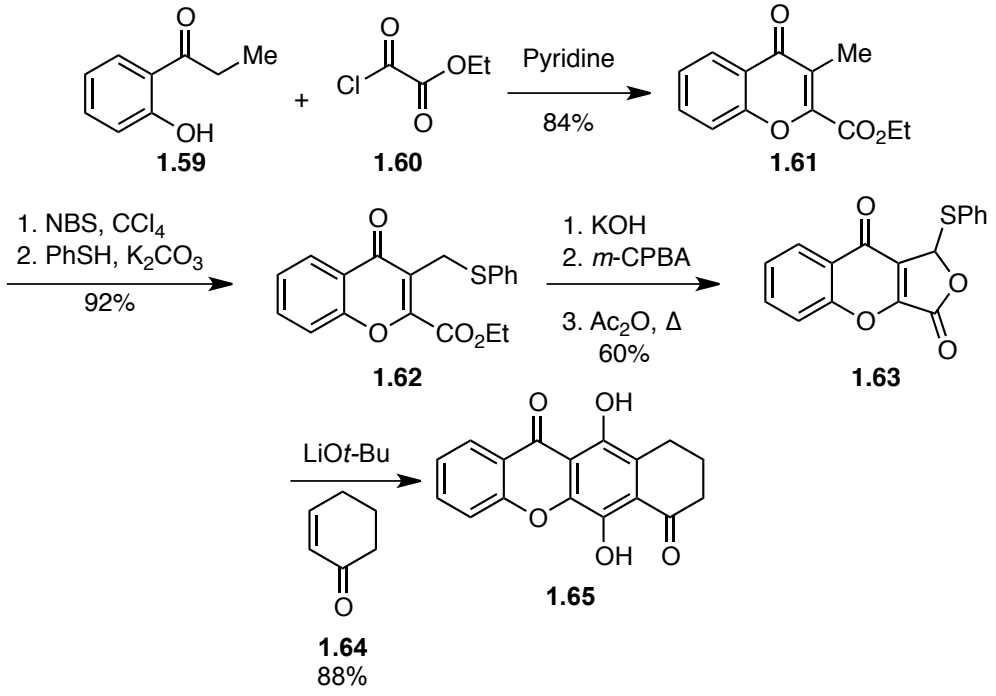


1.56 **1.57** **1.58**

1.2.6 The Hauser annulation

Hauser developed an approach to 1,4-dioxygenated xanthones using an annulation procedure that now bears his name (Scheme 1.10).[35] Phenylpropanone **1.59** was condensed with ethyl 2-chloro-2-oxoacetate (**1.60**) to provide chromone **1.61** in 84% yield. The methyl group of **1.62** was brominated under free radical conditions, and the bromide was displaced with PhSH to provide **1.63** in 92% overall yield. The methyl ester was saponified, and the sulfide was oxidized to the sulfoxide, which underwent a Pummerer rearrangement upon reaction with Ac_2O to provide **1.63** in 60% yield. Exposure of **1.63** to strongly basic conditions followed by reaction with cyclohexenone (**1.64**) induced the Hauser annulation to deliver xanthone **1.65** in 88% yield. Some significant disadvantages are associated with this methodology to the synthesis of 1,4-dioxygenated xanthones. First, the substrate scope used in the preliminary report included only four Michael acceptors. Additionally, the preparation of **1.63** required six steps, which limits the rate at which analogs could be generated.

Scheme 1.10 The Hauser annulation approach to xanthones



1.3 The Construction of 1,4-Dioxygenated Xanthone Natural Products

While the synthesis of 1,4-dioxygenated xanthones has been achieved with several methods, each has significant disadvantages such as low yielding reaction sequences or a high step count. However, some of the xanthone natural products in Figure 1.1 have been prepared, and within each total synthesis is a unique step in which the 1,4-dioxygenated xanthone is obtained. The synthesis of some of the natural products shown in Figure 1.1, and the routes by which the xanthones or quinone-xanthones were accessed, will be discussed in the following sections.

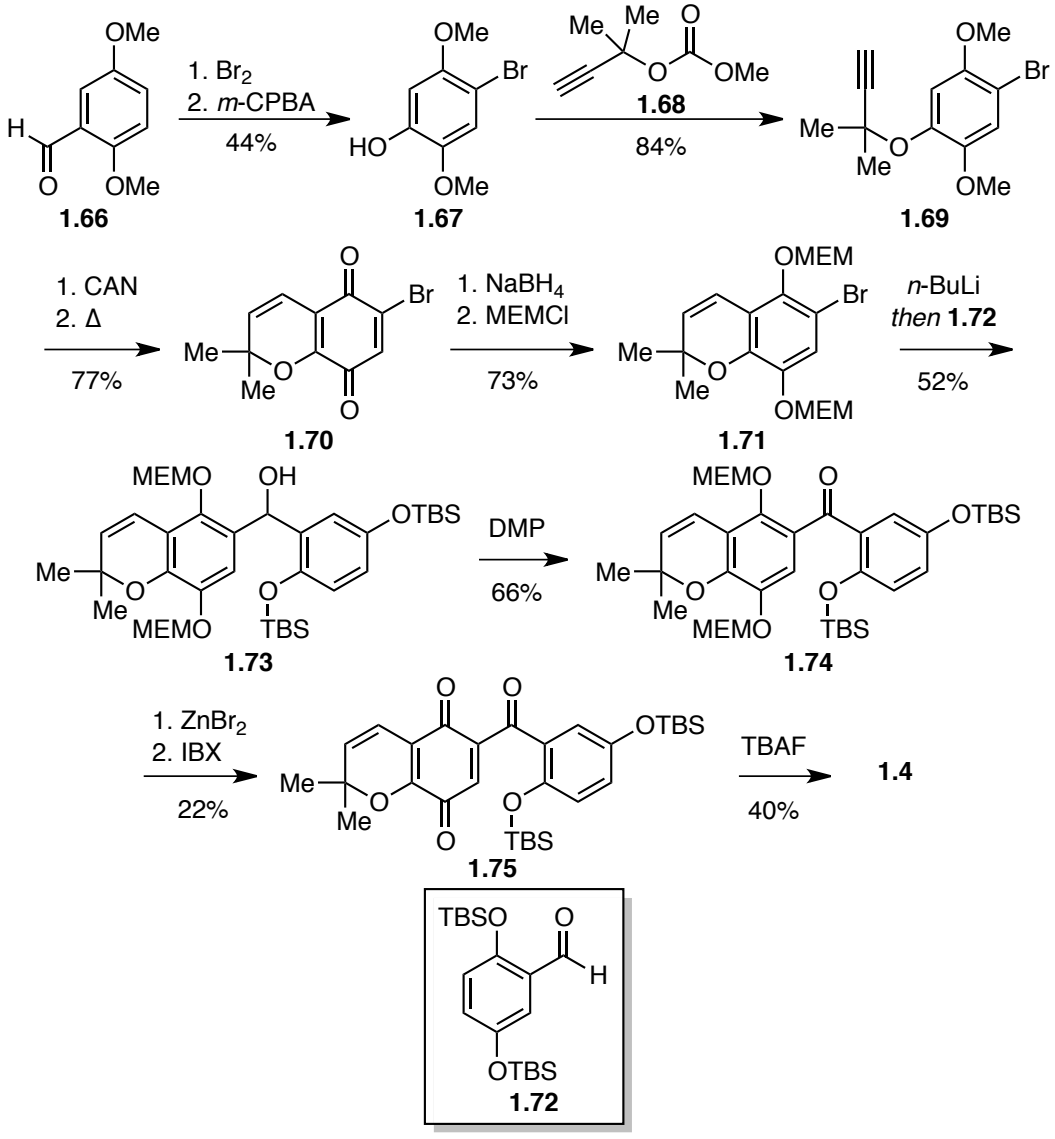
1.3.1 Atroviridin

1.3.1.1 Theodorakis' synthesis of atroviridin

Atroviridin (**1.4**) is one of a number of xanthones that has been isolated from the *Garcinia atroviridis* (Guttiferae) tree in Thailand.[5] The first reported synthesis of **1.4** was reported by Theodorakis and coworkers in 2003 (Scheme 1.11).[6] The synthesis began with the regioselective bromination of **1.66** followed by a Dakin oxidation of the resulting benzaldehyde to give the phenol **1.67** in 44% overall yield. The alkyne moiety in **1.68** was introduced by a copper catalyst[36] to give **1.69** in 84% yield. The dimethyl ether of **1.69** was oxidized to the quinone using ceric ammonium nitrate (CAN), and the resulting quinone was heated at high temperature to form the pyran ring *via* Claisen cyclization.[37] This two-step sequence to give the bicyclic compound **1.70** proceeded in 77% yield. The quinone moiety was then reduced with $NaBH_4$ in AcOH,[38] and the hydroquinone was protected as its MEM ether **1.71** in 73% yield. Exposure of **1.71** to *n*-BuLi induced a lithium/halogen exchange, and subsequent addition of aldehyde **1.72** delivered the benzylic alcohol **1.73** in 52% yield. The resulting alcohol was oxidized to the benzophenone **1.74** using Dess-Martin periodinane (DMP) in 66% yield.[39] In the final sequence of reactions, the MEM groups were removed with $ZnBr_2$, and the hydroquinone moiety was oxidized to the quinone **1.75** with 2-iodoxybenzoic acid (IBX) in a solution of DMF and $CHCl_3$[40] in 22% overall yield. Finally, the TBS group was removed with tetra-*n*-butylammonium fluoride (TBAF) to give the natural product **1.4** in 40% yield. While Theodorakis' preparation of **1.4** in 13 steps total and 12 steps in the longest linear sequence and 0.63% overall yield is noted for being the first synthesis, there were many problems with the sequence. Extensive manipulations of the hydroquinone by oxidation, reduction, and protection contributed in large measure to the total step count. Additionally, the yields of several transformations were low. The

preparation of the xanthone core by addition of an aryllithium into a functionalized benzaldehyde, oxidation to the benzophenone, and subsequent cyclization either by S_nAr or 1,4-addition is a common way to access 1,4-dioxygenated xanthones. It does have the benefit of a convergent synthesis by bringing two fragments together, but the step count for the preparation of the fragments oftentimes precludes the use of the strategy.

Scheme 1.11 Theodorakis' synthesis of atroviridin



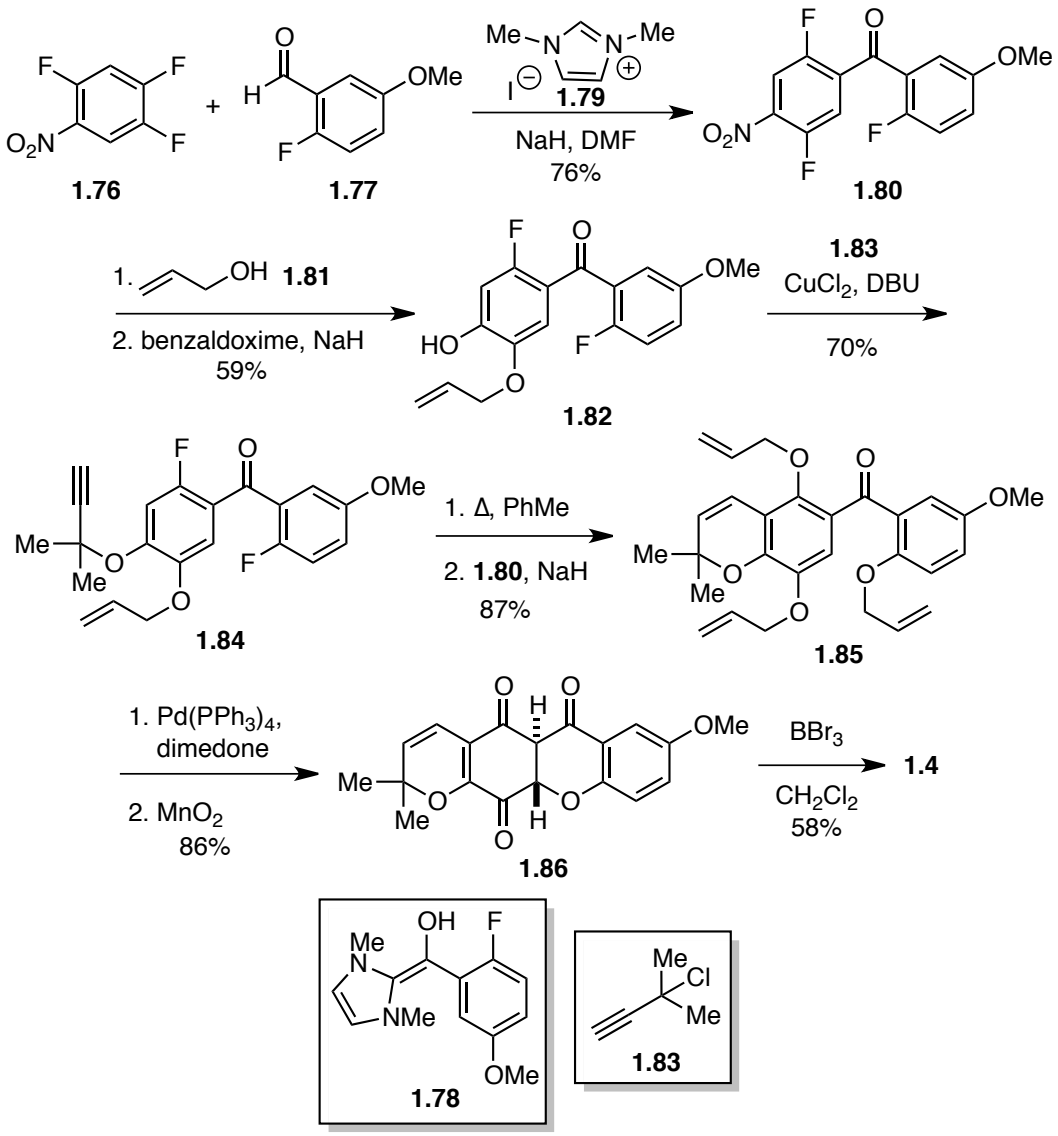
1.3.1.2 Suzuki's synthesis of atroviridin

Suzuki's synthesis of atroviridin is similar to that of Theodorakis, but the key step of the synthesis is the first step (Scheme 1.12).[7] Suzuki employed an *N*-heterocyclic carbene (NHC) catalyzed aroylation to prepare a benzophenone intermediate at the beginning of the synthesis. In the event, stirring a mixture of commercially available **1.77** in the presence of the *N*-heterocyclic carbene (NHC) **1.79** presumably formed the transient Breslow intermediate **1.78**. A nucleophilic aromatic substitution then occurred with nitroaromatic **1.76** to provide the benzophenone product **1.80** in 76% yield.[41] This was a much more effective entry to the benzophenone than the multi-step route Theodorakis used. With benzophenone in hand, Suzuki and coworkers continued with the rest of the synthesis.

A regioselective S_nAr of **1.80** using allyl alcohol (**1.81**) was performed to give the allylated product, which was then followed by displacement of the nitro group by the benzaldoxime anion[42] to give phenol **1.82** in 59% yield across two steps. The phenolic oxygen atom of **1.82** was alkylated with **1.83** in the presence of $CuCl_2$ to provide the alkylated compound **1.84** in 70% yield. In the next sequence of reactions, heating **1.84** induced cyclization of the side chain, and two S_nAr reactions were effected with the anion of **1.81** to furnish the allylated compound **1.85** in 87% yield. A global deallylation of **1.85** was achieved under palladium catalysis with dimedone as the nucleophile, and the resulting hydroquinone was oxidized to the quinone with MnO_2. Surprisingly, the phenolic oxygen atom underwent addition into the quinone in a conjugate manner to give the tetracyclic product **1.86** in 86% yield. Suzuki and coworkers reported that **1.86** was isolable and did not rearrange to the xanthone on silica gel. Finally, removal of the methyl group of **1.86** with BBr_3 was accompanied by rearrangement to the natural product **1.4** in 58% yield. The synthesis of **1.4** was achieved in nine steps in 13.7%

overall yield, which is a significant improvement over the previous synthesis. While the NHC catalyzed aroylation provided access to the benzophenone in one step without the use of strong bases or harsh Lewis acids, the substrate scope is limited to the use of highly fluorinated, expensive starting materials with restricted substitution patterns.

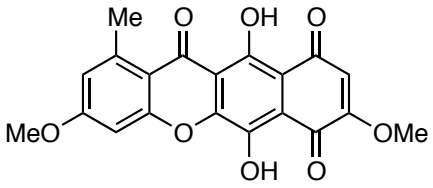
Scheme 1.12 Suzuki's approach to atroviridin



1.3.2 Bikaverin

Like numerous natural products in the literature, the xanthone bikaverin has a very interesting history. Kreitman and Nord first reported the isolation of a blood red pigment known as lycopersin in 1949.[43] Extensive degradation studies were performed on the pigment by the same group, and a tentative elemental composition of $C_{20}H_{15}O_8$ was proposed.[43,44] Interestingly, between 1950 and 1971, the same red pigment was isolated from four different culture media.[45] The structure was unequivocally solved by x-ray crystallography in 1972,[9] and the actual chemical composition for the compound was reported to be $C_{20}H_{14}O_8$. While the error in elemental composition was only a single hydrogen, the impact was significant. It was even believed that the natural product was a stable phenyl radical. Since the pigment was isolated from several bacterial cultures, many different names were associated with it. Finally, in 1971 Cornforth and coworkers named the compound bikaverin, and the synthetic community accepted it.[8] With the structure known numerous synthetic groups strived for the first total synthesis of the xanthone natural product.

Figure 1.2 The natural product bikaverin (**1.5**)



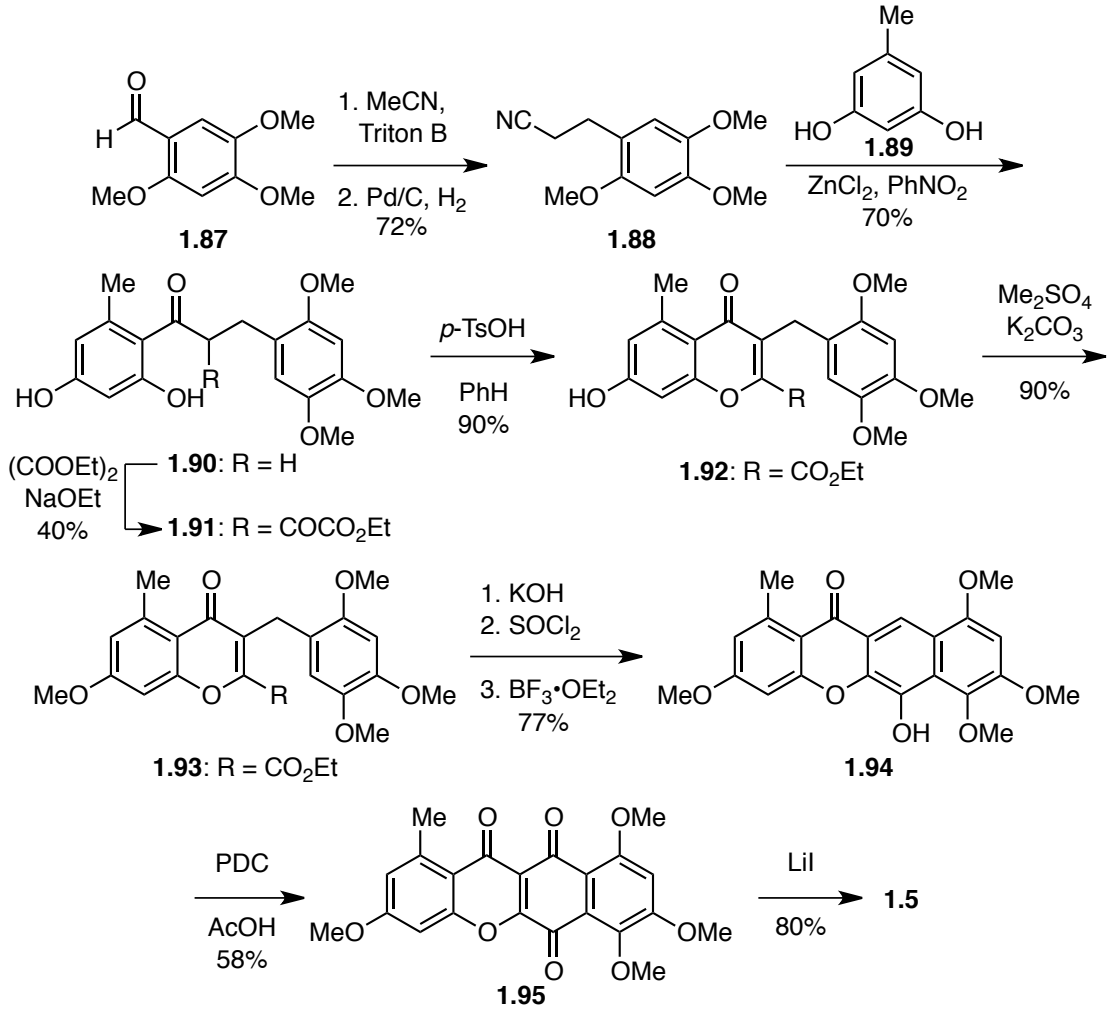
1.5

1.3.2.1 Barton's synthesis of bikaverin

Barton and coworkers reported the first synthesis of bikaverin in 1976.[45,46] Condensation of aldehyde **1.87** and MeCN with Triton B provided a conjugated nitrile that was then hydrogenated to provide **1.88** in 72% yield (Scheme 1.13). Activation of

the nitrile with $ZnCl_2$ was followed by a Houben-Hosch reaction with orcinol (**1.89**) as the nucleophile provided the aryl ketone **1.90** in 70% yield. Reaction of **1.90** with diethyl oxalate and excess NaOEt delivered the α-oxalate **1.91** in 40% yield, and cyclization of **1.91** to the chromone **1.92** occurred in 90% yield. The remaining phenol of **1.92** was then alkylated to the tetramethoxy compound **1.93** in 90% yield. The ethyl ester of **1.93** was saponified, the resulting carboxylic acid was converted to the acid chloride, and a Friedel-Crafts acylation was induced with BF_3•OEt_2 to give the tetracyclic xanthone core **1.94** in an impressive 77% yield. The carbon atom *para* to the phenol of **1.94** was oxidized with PDC in AcOH to the quinone **1.95** in 58% yield. Finally, demethylation of **1.95** was achieved with LiI to deliver the natural product **1.5** in 80% yield. Barton's synthesis of bikaverin is a terrific example of rational thinking and creative solving in the context of natural products. This route features an elegant cyclization to form the chromone **1.92**, as well as a high-yielding Friedel-Crafts reaction to form the tetracyclic core of the natural product. Although this was a well-designed synthesis of **1.5**, the multi-step sequence to the 1,4-dioxygenated xanthone precludes the use of this method in a general sense.

Scheme 1.13 Barton's synthesis of bikaverin



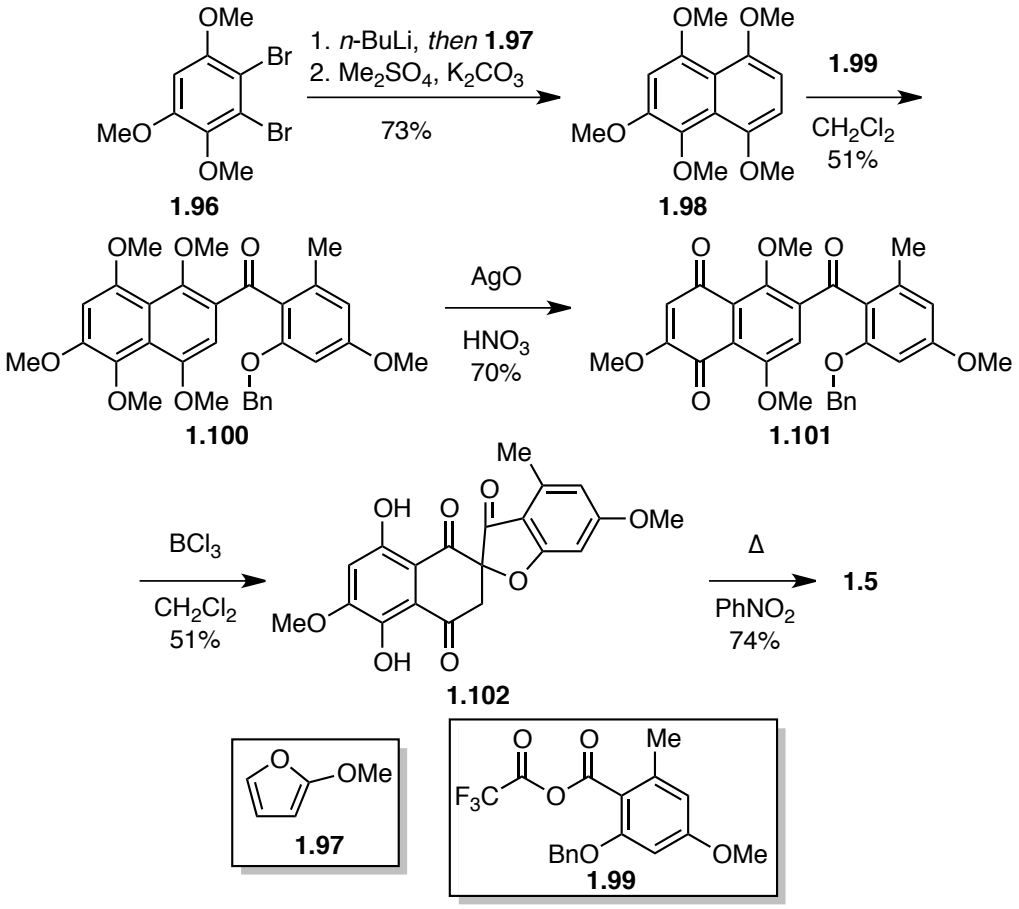
1.3.2.2 Giles' synthesis of bikaverin

Giles and coworkers were the third group to report a total synthesis of bikaverin **1.5** (Scheme 1.14).[47] Their synthesis of the natural product began with the reaction of the benzyne derived from **1.96** with 2-methoxyfuran (**1.97**). Subsequent methylation of the phenol delivered the pentamethoxynaphthalene **1.98** in 73% yield. A Friedel-Crafts reaction of **1.98** with freshly-prepared mixed anhydride **1.99** delivered the benzophenone **1.100** in 51% yield. Oxidation of the electron rich dimethyl ether of **1.100** with AgO

furnished the quinone **1.101** in 70% yield. The remaining dimethyl ethers were removed with BCl_3, and the resultant hydroquinone was oxidized to the quinone. The benzyl group of **1.101** was removed in the same reaction after which cyclization ensued and, surprisingly, the spirocycle **1.102** was isolated in 51% yield. Efforts to prevent the spirocyclization were unsuccessful. Heating the spirocycle under reflux in $PhNO_2$ effected rearrangement of **1.102** to **1.5** in 74% yield.

Notable features of this route include a benzyne cycloaddition to form the naphthalene core, a smaller step count to the target natural product compared to Barton's approach, and the first report of a spirocyclic intermediate *en route* to 1,4-dioxygenated xanthones. However, this is still not an efficient approach to the 1,4-dioxygenated xanthone for several reasons. The regioselectivity in the Friedel-Crafts acylation was poor in that the remaining mass balance was the undesired regioisomer. The rearrangement of the spirocycle **1.102** to the xanthone **1.5** took place in refluxing nitrobenzene, conditions that heat sensitive substrates would not withstand.

Scheme 1.14 Giles' synthesis of **1.5**

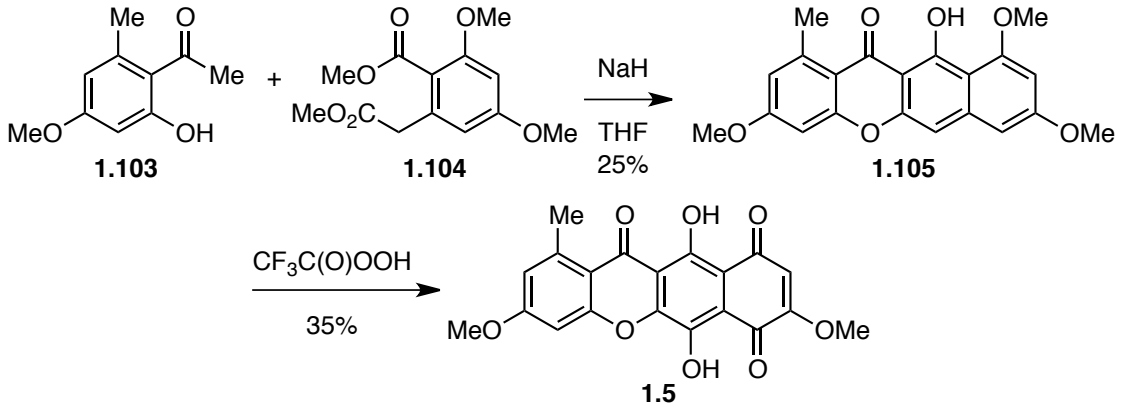


1.3.2.3 Kjær's synthesis of bikaverin

One of the shorter syntheses of bikaverin to date was reported by Kjær and coworkers (Scheme 1.15).[48] In the key step of the synthesis, stirring a mixture of acetophenone **1.103** with aryl ester **1.104**, which was available in three steps in 13% yield from commercial material, provided the tetracyclic xanthone **1.105** in 25% yield. The average yield of the reaction ranged from 20-25% even after optimization. The tetracyclic xanthone **1.105** was then exposed to trifluoroperacetic acid, delivering bikaverin (**1.5**) in 35% yield. A significant number of side products and recovered starting material made up the remaining mass balance of the reaction, which detracts

from the elegance of this approach. While the yields of the reactions were low, the innovation of this route rests in the quick access to the natural product and the ability to prepare structural analogs. That being said, low yields, and a restriction to tetracyclic xanthones preclude the use of this method to the preparation of other 1,4-dioxygenated xanthone derivatives.

Scheme 1.15 Kjær's synthesis of **1.5**

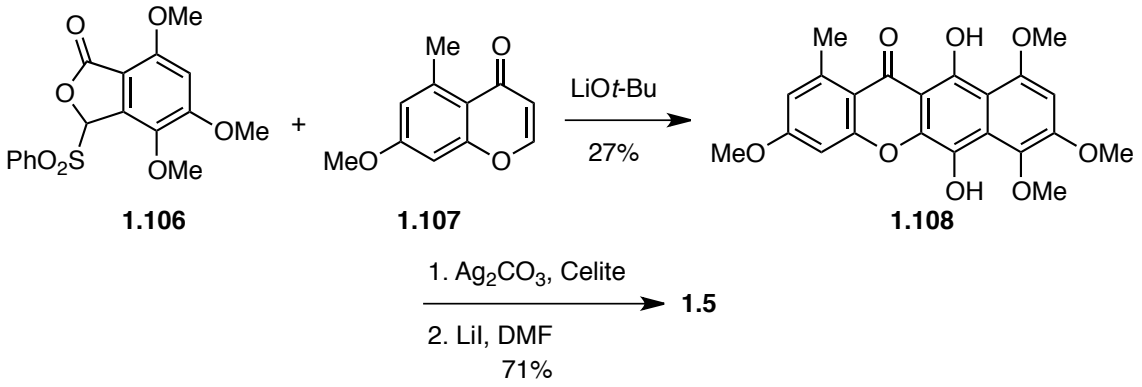


1.3.2.4 Hauser's synthesis of bikaverin

Hauser developed an approach to bikaverin using his annulation procedure (Scheme 1.16).[49] In the key step, sulfone **1.106** was treated with LiO*t*-Bu to generate an anion that then reacted in a conjugate manner with chromone (**1.107**) to give, after extrusion of CO_2, xanthone **1.108** in 27% yield. The hydroquinone **1.108** was oxidized to the quinone using Fetizon's reagent, and the methoxy groups were demethylated with LiI in DMF to give the natural product bikaverin (**1.5**) in 71% overall yield. The innovation of this chemistry is the extension of his annulation reaction to the preparation of complex 1,4-dioxygenated xanthone natural products. While bikaverin (**1.5**) was prepared in relative few steps, the yields of the annulation step for the reported examples are quite

low, and the preparation of analogs of the sulfone **1.106** to access analogs of the natural product oftentimes requires several steps.

Scheme 1.16 Hauser's annulation approach to bikaverin

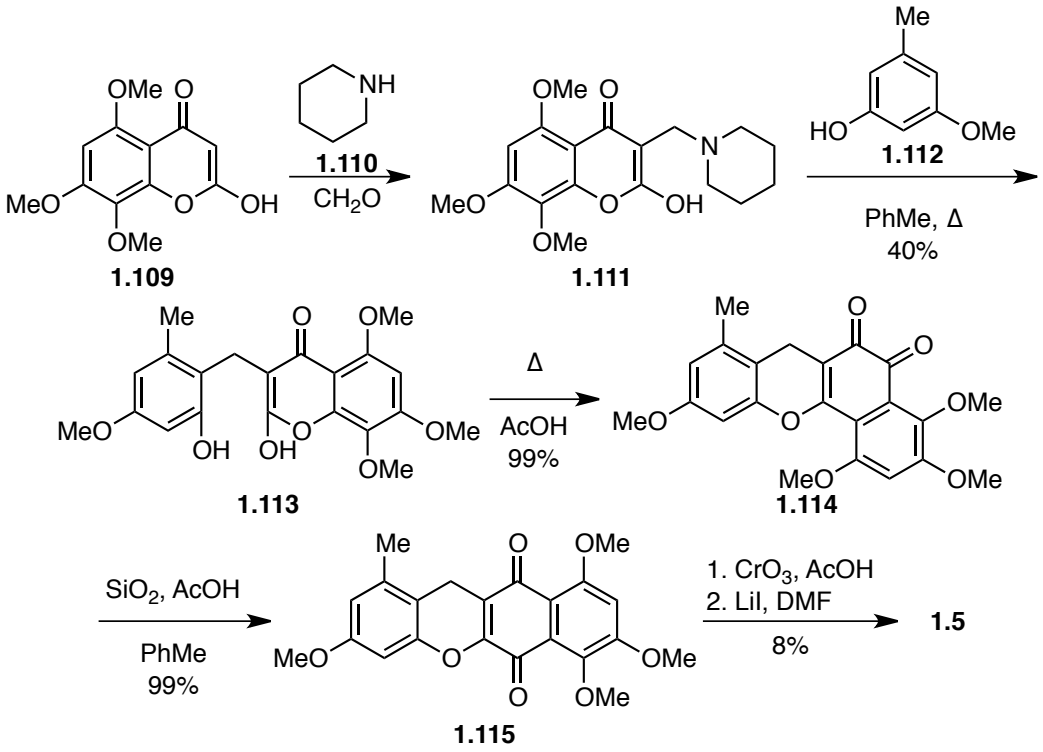


1.3.2.5 Plat's synthesis of bikaverin

Plat and coworkers also developed an approach to bikaverin (**1.5**) (Scheme 1.17).[50] Condensation of piperidine (**1.110**) with formaldehyde generated an iminium ion that underwent reaction with **1.109** to give the Mannich base **1.111**. Reaction of **1.111** and phenol **1.112** delivered the alkylated compound **1.113** in 40% yield. Heating **1.113** in AcOH delivered the *o*-quinone **1.114**, which was then isomerized under mildly acidic conditions to the tetracyclic xanthene **1.115** in >99% yield over two steps. The key step in the synthesis was the oxidation of the xanthene **1.115** to the xanthone. Surprisingly, typical oxidation reagents such as DDQ or CAN did not promote the transformation. Plat found that only rapid exposure of **1.115** to chromic acid provided the desired xanthone in 10% yield. Demethylation of the xanthone to bikaverin was accomplished with LiI in 78% yield. Although the strategy of oxidizing a xanthene to a xanthone has been reported in the literature,[15] the application to 1,4-dioxygenated xanthone natural products

is noteworthy, but the low yielding oxidation precludes the use of this method to the synthesis of other xanthone natural products.

Scheme 1.17 Plat's synthesis of bikaverin



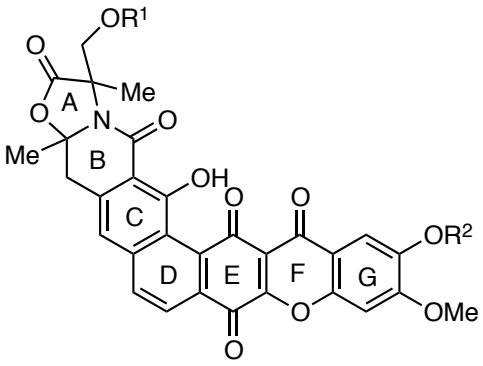
1.3.3 Citreamicin α

The citreamicin family of natural products comprises seven compounds with many structural features in common (Figure 1.3). Introduced to the scientific community in 1989, the citreamicin antibiotics have piqued the interest of synthetic groups and a number of interesting studies about the biological activity[10] and biosynthesis[51] have been published. Citreamicins α, β, γ, ζ, and η (**1.6**, **1.116**-**1.119**) have in common a heptacyclic, angularly fused quinone-xanthone core with oxygenation on the terminal aromatic ring in the form of a methoxy group or phenol. Citreamicin δ and ε (**1.120** and **1.121**) were discovered in 2008.[52] Citreamicin δ differs from the other citreamicins due

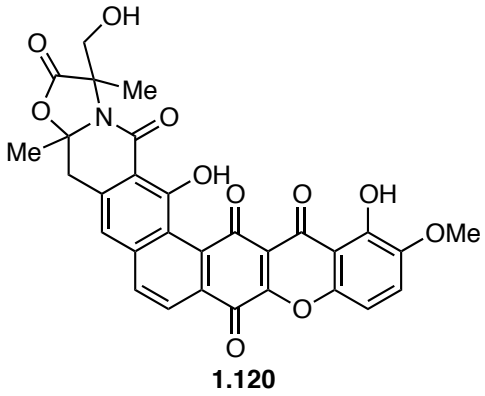
to the location of oxygenation on the G-ring in addition to a free alcohol in the oxazolidinone A-ring. Citreamicin ε (**1.121**) is unique among the remaining family members for several reasons: the natural product exists at the xanthone oxidation state rather than a quinone xanthone, the phenolic oxygen atom on the G-ring is at a regioisomeric position compared to the other family members, and the D-ring of **1.121** contains a unit of saturation. While the structural attributes are impressive, the biological activity of the citreamicins is equally so. Citreamicin α (**1.6**) is active against human colon and lung cancers with an MIC of 4 nM, and has an *in vitro* activity of 15 ng/mL against several Gram-positive bacteria.[52] The two newest citreamicin members **1.120** and **1.121** possess slightly lower activity against Gram-positive bacteria with an MIC of 60 ng/mL, which compares favorably to two FDA approved Gram-positive antibiotics.[52] Citreamicins **1.120** and **1.121** were found to be active against many antibiotic resistant bacteria and exhibit cytotoxic properties, making them potential anticancer agents.

To date, no syntheses of any of the citreamicins have been reported, but the biological properties alone make these potential antibiotic agents. The citreamicins are structurally very similar to cervinomycin A_2 (**1.122**) with the only difference being a lack of functionalization on the oxazolidine A-ring. Cervinomycin A_2 is highly active against anaerobic and Gram positive bacteria, and to date two syntheses have been reported by the groups of Kelly[53] and Rao,[54] and a synthesis of the cervinomycin A_2 methyl ether was reported by Mehta.[55-57] Each synthesis developed a noteworthy approach to the xanthone portion of the natural product.

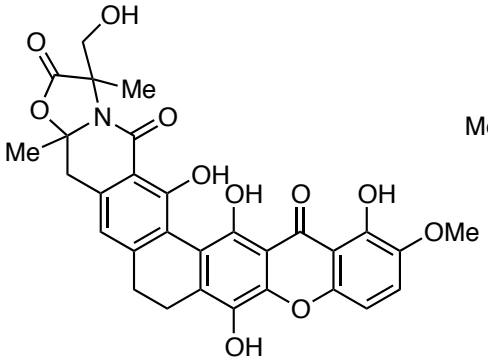
Figure 1.3 Citreamicin natural products **1.6**, **1.116**-**1.121** and cervinomycin A_2 (**1.122**)



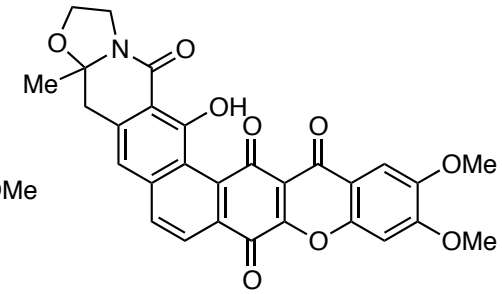
1.6: $R^1 = COCH_2CH(CH_3)_2$ R^2 = Me
1.116: $R^1 = COCH(CH_3)_2$ R^2 = Me
1.117: $R^1 = COCH_3$ R^2 = Me
1.118: $R^1 = COCH_2CH(CH_3)_2$ R^2 = H
1.119: R^1 = H R^2 = Me



1.120



1.121



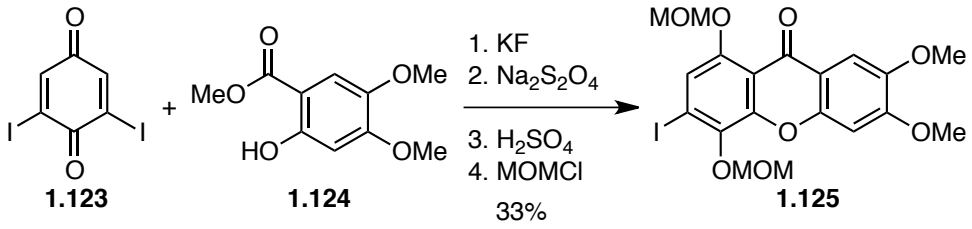
1.122

1.3.3.1 Kelly's synthesis of cervinomycin A_2

The first steps in Kelly's total synthesis of cervinomycin A_2 (**1.122**) were focused on the preparation of the xanthone fragment (Scheme 1.18).[53] A solution of iodoquinone **1.123** and salicylate **1.124** was stirred in the presence of KF, following the precedent of Brassard[24] (*cf*. Scheme 1.5), effecting an addition/elimination sequence to give the alkylated product. The quinone was then reduced to the hydroquinone with $Na_2S_2O_4$, cyclization to the xanthone was effected with concentrated H_2SO_4, and the phenolic

oxygen atoms of the hydroquinone were protected as their MOM ethers. This four-step sequence to the xanthone **1.125** was performed in 33% overall yield.

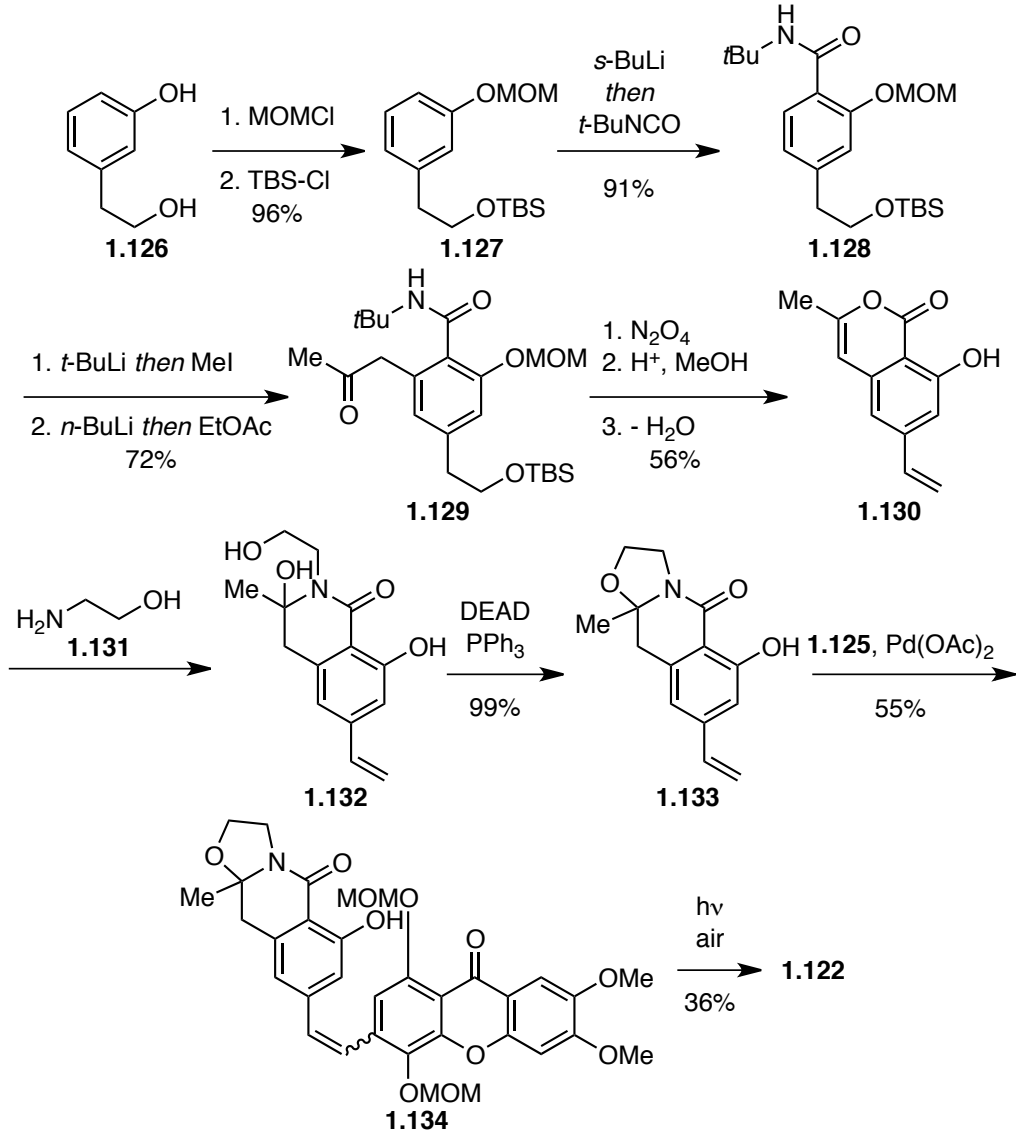
Scheme 1.18 Kelly's synthesis of xanthone **1.125** using an iodoquinone



With the xanthone fragment **1.125** in hand, Kelly and coworkers turned their attention to the preparation of the oxazolidine-containing fragment (Scheme 1.19). A selective MOM protection of the phenol group of **1.126** followed by protection of the alcohol as its TBS ether gave **1.127** in 96% yield. A regioselective directed metalation of **1.127** with *s*-BuLi followed by reaction with *t*-BuNCO provided the amide **1.128** in 91% yield. The metalation-directing properties of the aryl amide group aided the next steps of the sequence. First, directed metalation *ortho* to the amide was followed by reaction with MeI. An equivalent of acetone was then added to the aryl methyl group by Claisen condensation of the methyl anion of **1.128** with EtOAc to deliver the bicyclic product **1.129** in 72% overall yield. The aryl amide was converted to the benzoic acid with N_2O_4,[58-60] the acid labile groups were removed with acidic MeOH, and the homobenzylic alcohol was eliminated as its phenylselenoxide derivative[61] to give the styrene **1.130** in 56% yield. Reaction of **1.130** with ethanolamine (**1.131**) delivered the amide **1.132** in 80% yield. The primary alcohol of **1.132** was displaced under Mitsunobu conditions to furnish the oxazolidine **1.133** in 99% yield. The penultimate step of the synthesis involved a palladium-catalyzed Heck reaction with iodoxanthone **1.125**, which delivered **1.134** in 55% yield. Irradiation of **1.134** set off a sequence of reactions including closure

of the final ring of the natural product, removal of the MOM protecting groups, and oxidation of the resulting hydroquinone to the quinone. This entire transformation proceeded in 36% yield to deliver cervinomycin A_2 (**1.133**). In total, the synthesis was achieved in 3.8% overall yield requiring 18 total steps with 12 as the longest linear sequence. Key steps of the reaction include an elegant application of Brassard's method to 1,4-dioxygenated xanthones, a Claisen reaction of **1.128** with EtOAc to provide the methyl ketone **1.129**, and the displacement of the primary alcohol of **1.132** under Mitsunobu conditions. The installation of the A-ring of cervinomycin A_2 (**1.122**) with **1.131** was adopted by the future syntheses of the natural product. Kelly's synthesis of **1.122** is noted for it being the first synthesis; however, the formation of the styrene derivative **1.133** required numerous steps, and the final step of the sequence proceeded in only 36% yield.

Scheme 1.19 Kelly's synthesis of cervinomycin A_2

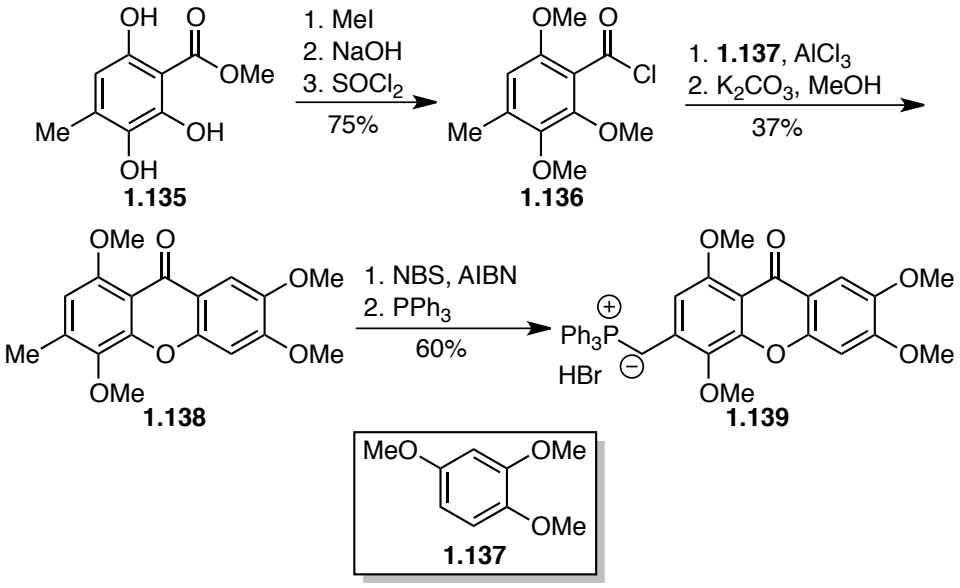


1.3.3.2 Mehta's synthesis of cervinomycin A_2 methyl ether

Mehta and coworkers had a different strategy by which to access the cervinomycin A_2 core (Scheme 1.20).[55-57] Beginning with triphenol **1.135**, permethylation with MeI, saponification of the methyl ester, and formation of the acid chloride gave **1.136** in 75% yield. The xanthone portion of the natural product was then

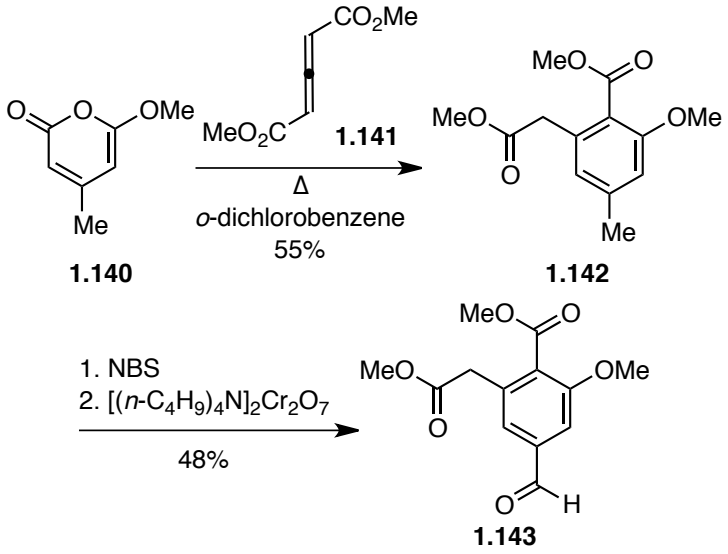
prepared using a Friedel-Crafts reaction. In the event, acylation of 1,2,4-trimethoxybenzene (**1.137**) with acid chloride **1.136** was achieved with $AlCl_3$ as the Lewis acid. A phenolic oxygen atom of the intermediate benzophenone was deprotected in the reaction as well due to the presence of excess $AlCl_3$. Cyclization of the phenol under basic conditions delivered the xanthone **1.138** in 37% yield. The aryl methyl group was brominated under free radical conditions and the intermediate bromide was treated with PPh_3 to deliver the Wittig salt **1.139** in 60% yield across two steps.

Scheme 1.20 Mehta's synthesis of the Wittig salt **1.139**



The synthesis of the aldehyde partner for the upcoming Wittig reaction began with a Diels-Alder cycloaddition between α-pyrone **1.140** and ketene **1.141**, followed by decarboxylation at elevated temperatures to give the highly functionalized aromatic ring **1.142** in 55% yield (Scheme 1.21). The aryl methyl group underwent free radical bromination followed by oxidation of the resulting bromide with bis(tetrabutylammonium) dichromate to the aldehyde **1.143** in 48% yield. With the Wittig precursors in hand, the pivotal coupling reaction was explored.

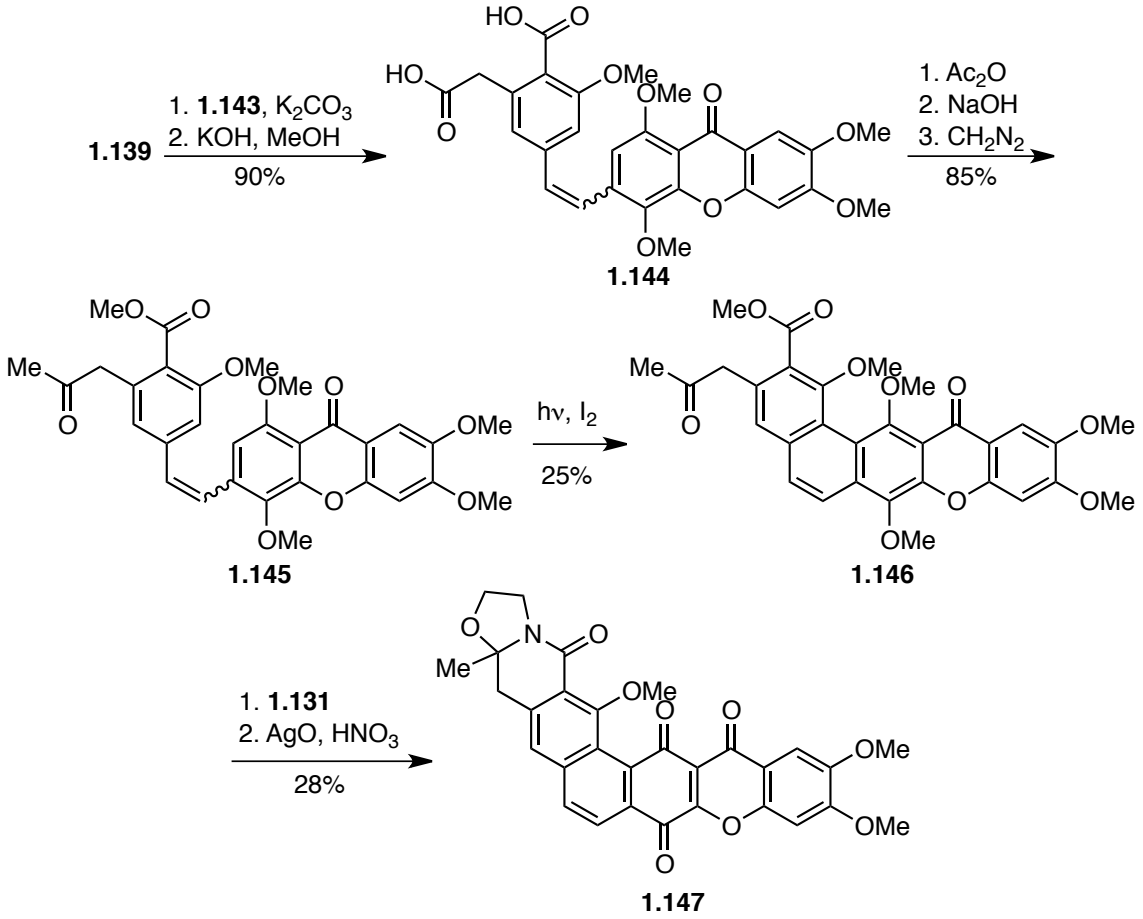
Scheme 1.21 Mehta's Diels-Alder approach to aldehyde **1.143**



Reaction of **1.139** with K_2CO_3 and aldehyde **1.143** delivered the stilbene derivative **1.144** in 90% yield after saponification of the methyl esters (Scheme 1.22). In a series of three steps, the benzoic acid of **1.144** was transformed into the aryl ester, and the carboxylic acid of **1.144** was activated as the mixed anhydride, which underwent attack by CH_2N_2 to give the methylated product **1.145** in 85% yield. The key step of the synthesis was similar to that of Kelly's photolytic step. Irradiation of **1.145** in the presence of I_2 delivered the xanthone **1.146** in 25% yield, and reaction of **1.146** with ethanolamine (**1.131**) formed the oxazolidine ring. The final step of the synthesis was oxidation of the dimethyl-protected hydroquinone to the quinone **1.147** in 28% yield. The undesired methyl group could not be removed, thus the authors completed the synthesis of cervinomycin A_2 methyl ether. The synthesis of **1.146** was accomplished in 22 total steps with 19 as the longest linear sequence. A notable feature of the route includes a Wittig reaction to couple the phosphonium salt and aldehyde fragments together as well as a unique photo-induced ring closure. There are two notable drawbacks to the synthesis. First, the xanthone **1.139** was prepared using Friedel-Craft

chemistry in only 37% overall yield. Second, the yields of several transformations are either not included or very low.

Scheme 1.22 Mehta's completion of cervinomycin A_2 methyl ether

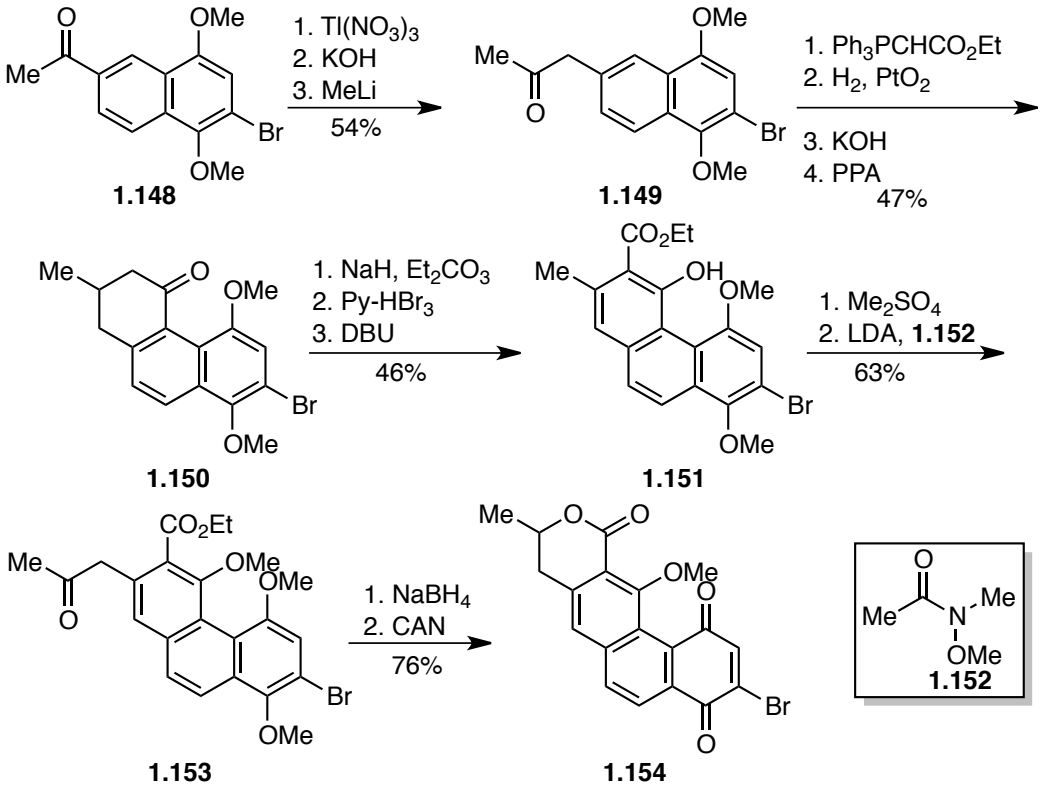


1.3.3.3 Rao's synthesis of cervinomycin A_2

Rao and coworkers published the second total synthesis of **1.122** in 1991 (Scheme 1.23).[54] The synthesis began with the three step conversion of **1.148** to the methyl ketone **1.149** in 54% overall yield. A Wittig reaction of the methyl ketone, followed by hydrogenation of the resulting olefin, saponification of the methyl ester, and then electrophilic aromatic substitution reaction with PPA delivered the acetophenone **1.150** in

47% yield. Treatment of **1.150** with diethylcarbonate under basic conditions gave an ethyl ester. The benzylic position of **1.150** was brominated with pyridinium tribromide, and the resulting benzyl bromide was eliminated with DBU to give the aromatized tricycle **1.151** in 46% yield. The phenol of **1.151** was then methylated with Me_2SO_4. The aryl methyl group was deprotonated with LDA, and subsequent reaction with Weinreb amide **1.152** furnished the methyl ketone **1.153** in 63% yield. Reduction of the ketone to the alcohol resulted in cyclization to the lactone, and the dimethyl-protected hydroquinone was oxidized with CAN to the quinone **1.154** in 76% yield.

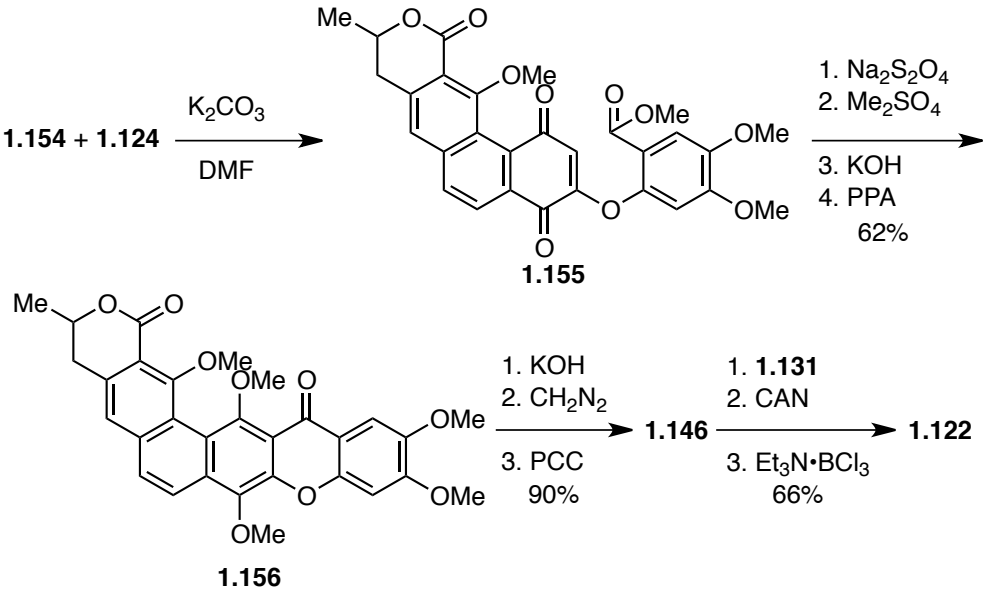
Scheme 1.23 Rao's synthesis of bromoquinone **1.154**



The remaining steps in Rao's synthesis are shown in Scheme 1.24. Following the precedent of Brassard and coworkers,[24] reaction of the bromoquinone **1.154** with

salicylate **1.124** under basic conditions delivered the alkylated quinone **1.157** in an unreported yield. The quinone was reduced with $Na_2S_2O_4$, the hydroquinone was protected as the dimethyl ether, the aryl ester was saponified to the benzoic acid, and the cyclization to the xanthone **1.156** was induced by heating in PPA in 62% overall yield. Rao and coworkers then converted **1.156** to **1.146** by opening the lactone, methylation of the benzoic acid, and oxidation of the secondary alcohol to the ketone **1.146** in an impressive 90% overall yield. Finally, reaction of **1.146** with ethanolamine **1.131** formed the oxazolidine, the hydroquinone was oxidized to the quinone with CAN, and the aryl methyl group that gave Mehta trouble was removed with $Et_3N{\bullet}BCl_3$ to deliver **1.122** in 66% yield. The synthesis of **1.122** was achieved in 29 total steps with 26 in the longest linear. Notable features of Rao's approach include the one-carbonyl homologation of acetophenone **1.148** to the methyl ketone **1.149**, an application of Brassard's addition/elimination sequence to the xanthone core,[24] and a successful demethylation of advanced intermediate **1.146** with $Et_3N{\bullet}BCl_3$. Compared to Kelly's synthesis, the effort by Rao and coworkers is significantly longer and is less efficient in terms of step count. Many important reactions, in particular the reaction sequence to form the xanthone, were low yielding or not reported.

Scheme 1.24 Rao's completion of **1.122**

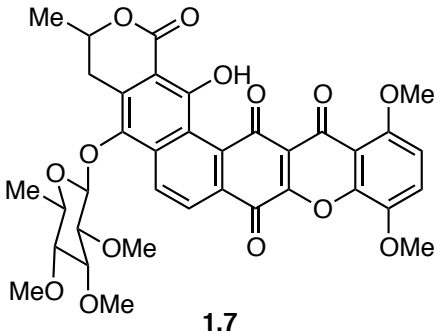


1.4 THE MARTIN GROUP'S APPROACH TO IB-00208

The quinone xanthone IB-00208 (**1.7**) was isolated in 2003 from the culture broth *Actinomadura* by Romero and coworkers (Figure 1.4). The biological activity in addition to its complex molecular architecture made it a compelling target for total synthesis. To date, no syntheses of **1.7** have been reported; however, the Martin group has had an interest in the natural product over the past several years. The previously discussed approaches to 1,4-dioxygenated xanthones and quinone xanthones are plagued with high step counts, low yielding sequences, and harsh reaction conditions that would not be amenable to the preparation of **1.7** and related analogs. We recognized the paucity of efficient methods to access the xanthone core, thus we initiated a program to develop a novel strategy by which IB-00208 and similarly complex xanthone natural products could be obtained quickly and from readily available starting materials. If a general strategy could be developed and successfully applied to the preparation of **1.7**, then we could in

principle apply the approach to several other xanthone natural products such as citreamicin α (**1.6**).

Figure 1.4 The quinone xanthone IB-00208



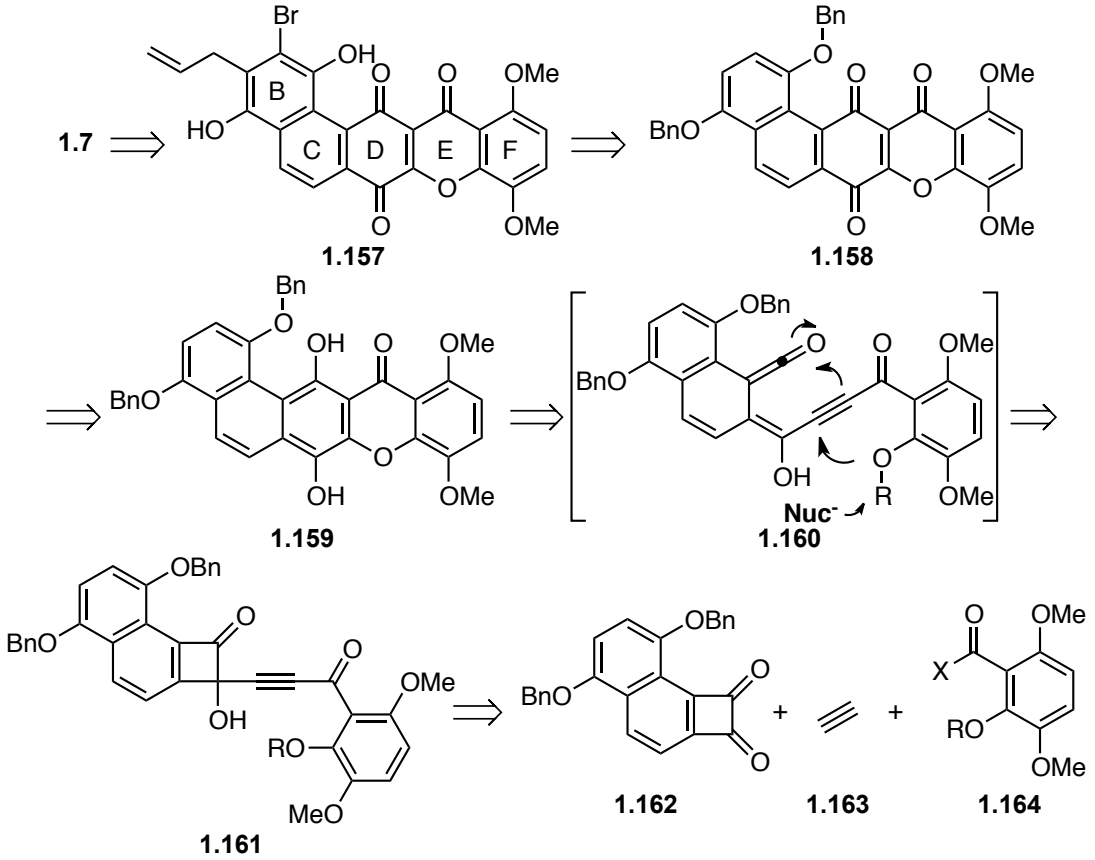
1.7

1.4.1 The Martin group's retrosynthesis of IB-00208

The retrosynthesis of IB-00208 shown in Scheme 1.25 was proposed by Dr. Douglas Mans. The A-ring of the natural product **1.7** would be obtained after functionalization of the B-ring of **1.157**. Dr. Mans proposed that the allyl group of **1.157** would undergo a Wacker oxidation to the methyl ketone, installation of the sugar subunit onto the less sterically encumbered phenolic oxygen atom of the B-ring, a Corey-Bakshi-Shibaki reduction to the alcohol, and then carbonylative cyclization under palladium catalysis. Pentacycle **1.157** would be obtained from **1.158** after hydrogenolysis of the benzyl ethers, regioselective allylation of the more accessible phenolic oxygen atom of **1.158**, regioselective bromination *ortho* to the phenolic moiety, and then an aromatic Claisen rearrangement. The quinone xanthone **1.158** would arise from oxidation of the hydroquinone moiety of the 1,4-dioxygenated xanthone **1.159**. A key step in the proposed synthesis of **1.7** is the formation of 1,4-dioxygenated xanthone **1.159** from ynone **1.161**. Upon thermolysis of **1.161**, the cyclobutenone moiety would undergo ring opening, following the precedent of Moore and coworkers,[62,63] to the ketene intermediate

1.160. From ketene **1.160**, we envisioned that unmasking of the phenolic oxygen atom by an exogenous nucleophile would set off a sequence of cyclization reactions in which the oxygen atom would cyclize onto the alkyne with further cyclization onto the ketene. This portion of the key step was inspired by the work of Fuganti.[64,65] Ynone **1.161** is readily available from the combination of benzocyclobutenedione **1.162**, acetylene (**1.163**), and an acyl aromatic **1.164**.[66] The sequential Moore rearrangement followed by the cyclization first reported by Fuganti has not been reported in the literature, so it offers us an opportunity to expand the scope of both reactions and apply them to the field of xanthone synthesis.

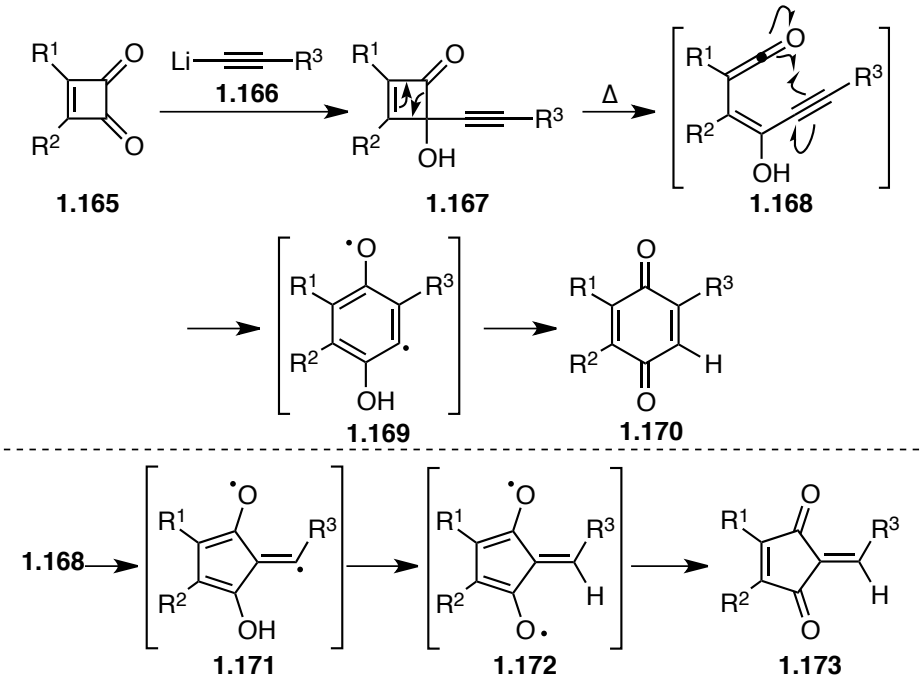
Scheme 1.25 Martin group's cyclization strategy to IB-00208



1.4.2 The Moore rearrangement

In the mid 1980's, Moore and coworkers published a method to access highly functionalized quinones from readily available materials (Scheme 1.26).[62] In this sequence, reaction of an acetylide nucleophile **1.166** with a squarate[67-70] such as **1.165** generates a relatively unstable alcohol **1.167**. Upon heating, **1.167** undergoes a 4π electrocyclic cyclobutene ring opening to deliver a reactive ketene intermediate **1.168** that cyclizes in a 6-*exo*-dig fashion to provide a diradical intermediate **1.169**. Abstraction of a hydrogen atom of **1.169** in an intermolecular fashion delivers quinone **1.170**. Moore[63,71,72] and others[73,74] have performed numerous elegant mechanistic and computational[75,76] studies that support a diradical process to **1.169**. For compounds with alkyl groups substituted at the R^3 position of **1.167**, the quinone is the exclusive product from the rearrangement. If the alkyne nucleophile is substituted with a phenyl or carbonyl containing functional group, the five-membered cyclopentanedione **1.173** is the preferred product, although the quinone is sometimes obtained.[62] It is believed that this shift in reactivity arises from the radical stabilizing properties of an aromatic (or carbonyl) group at the R^3 position in intermediate **1.171**. Once the five membered diradical species **1.171** is formed, hydrogen atom abstraction would generate **1.172**, which is at the same oxidation level as **1.173**. A review of the Moore rearrangement, the reactivity of squarates such as **1.167**, and the numerous mechanistic studies that were used to probe the mechanism was recently reported by Dr. Daniel Knueppel.[77]

Scheme 1.26 The Moore rearrangement

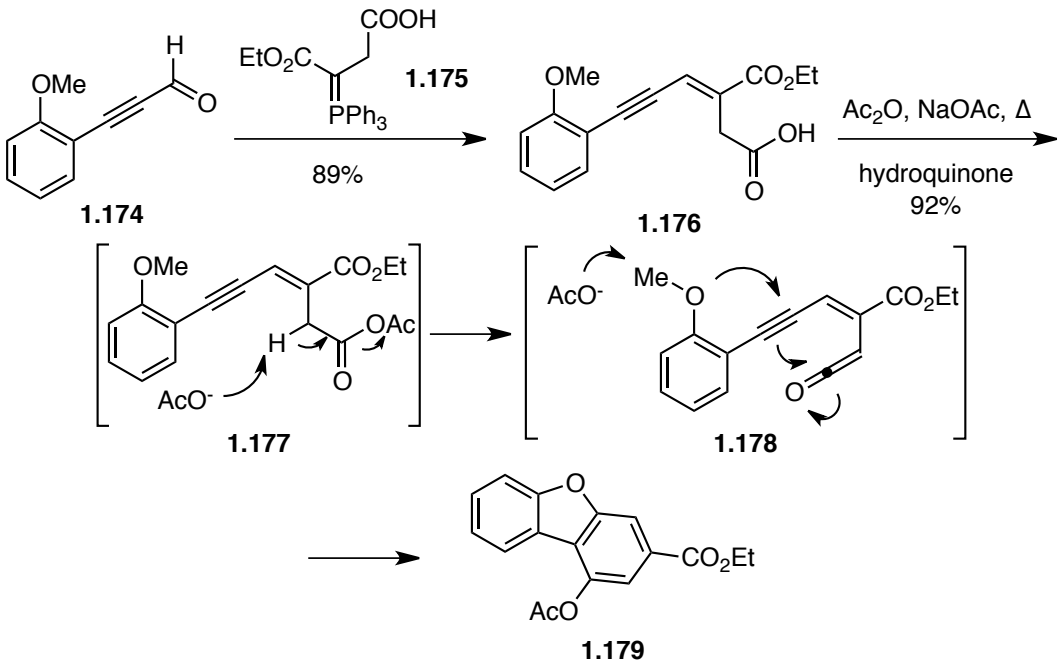


1.4.3 Cyclization onto the alkyne inspired by Fuganti

In 2003, Fuganti described an efficient method to access substituted dibenzofurans featuring a benzannulation reaction.[65] The dibenzofuran moiety is found in numerous natural products, with many exhibiting antifungal and antibiotic properties.[78,79] The sequence of reactions that inspired Dr. Mans to include this chemistry in the approach to IB-00208 is shown in Scheme 1.27. The alkynyl aldehyde **1.174** underwent a highly stereoselective[80,81] Wittig reaction with phosphonium ylide **1.175** to the *E*-succinic acid **1.176** in 89% yield. Exposure of **1.176** to Ac_2O formed a mixed anhydride **1.177**, which underwent loss of acetate to form the intermediate ketene **1.178**. Demethylation in the presence of excess acetate unmasks the latent phenoxide, which then cyclizes onto the alkyne with subsequent cyclization onto the ketene to deliver the dibenzofuran **1.179** in 92% yield. The cyclization was performed in the presence of 1,4-

hydroquinone, which presumably reacts with any radicals that are formed at the elevated temperatures of the reaction. Fuganti has published other applications of this reaction.[64,82,83]

Scheme 1.27 Dibenzofuran synthesis by benzannulation



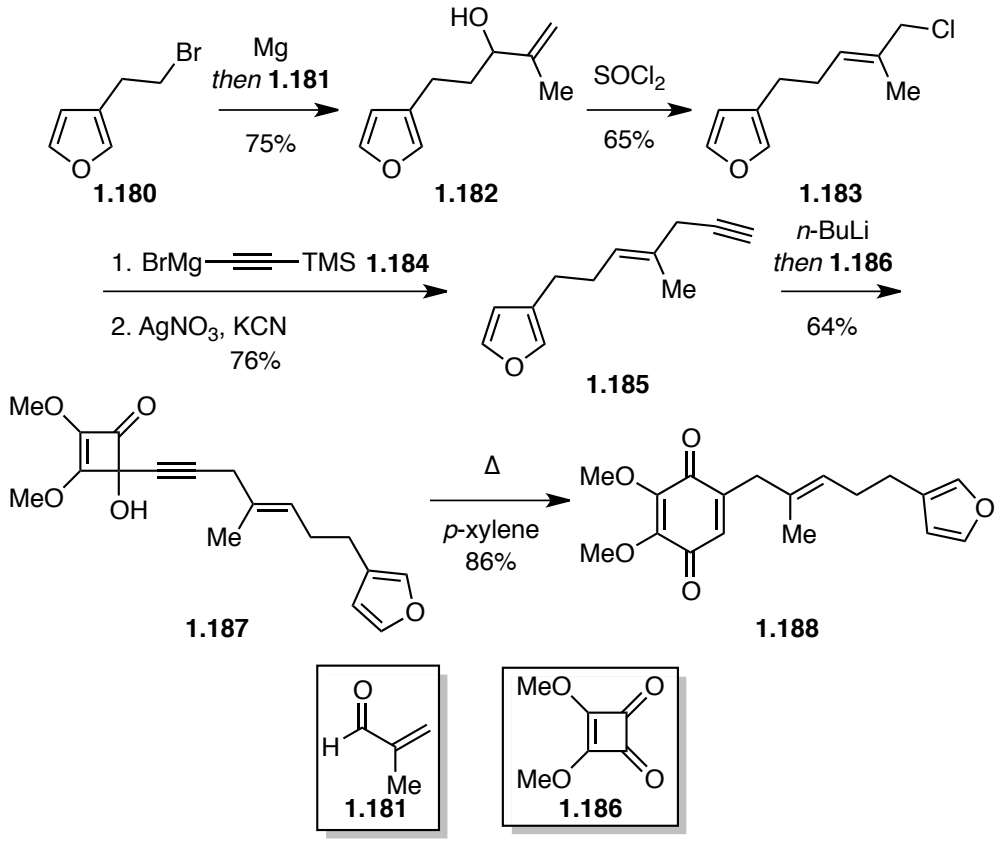
The Moore rearrangement has seen several uses in the context of complex quinone natural products. In many of the reported examples, traditional methods to obtain quinones, such as oxidation of the hydroquinone moiety, would have been less efficient. Selected examples of syntheses using the Moore rearrangement as a key step of the sequence will be discussed in the following section.

1.5 The Moore Rearrangement in Total Synthesis

In 1989, Moore and coworkers disclosed the first total synthesis of isoarnebifuranone (**1.188**) using their methodology (Scheme 1.28).[84] Isoarnebifuranone is traditionally known as a pain killer in the Chinese culture, and it was reported to be

linked to the inhibition of prostaglandin biosynthesis.[85,86] The synthesis of **1.188** began with the Grignard reaction of furanyl bromide **1.180** with aldehyde **1.181** to deliver the allylic alcohol **1.182** in 75% yield. Chlorination of **1.182** with $SOCl_2$ provided the isomerized primary chloride **1.183** in 65% yield. Displacement of the chloride ion with **1.184** in the presence of a copper source delivered the alkynylated product, that was subsequently converted to the terminal alkyne **1.185** in 76% overall yield. Formation of the lithium acetylide followed by reaction with dimethylsquarate (**1.186**) delivered the desired product **1.187** in 64% yield. The Moore rearrangement of **1.187** was induced in *p*-xylene under reflux to deliver the natural product **1.188** in 86% yield. This was an elegant application of the Moore rearrangement to the synthesis of a natural product, and the final product was obtained in only eight steps in 20% overall yield.

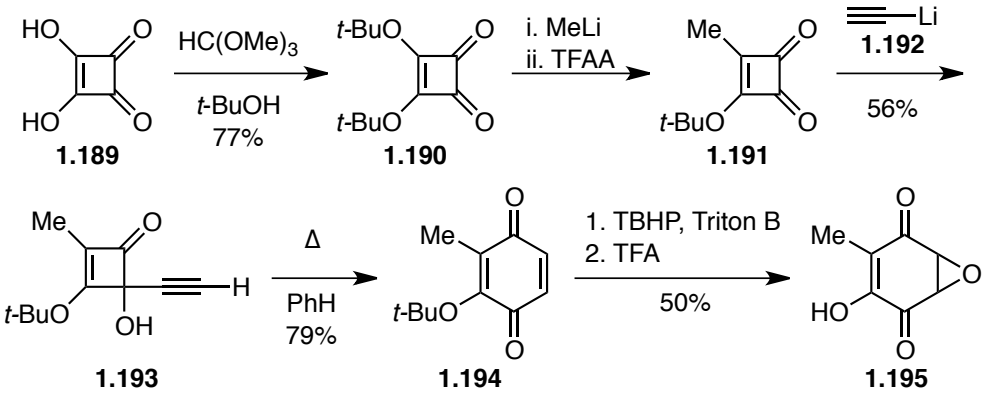
Scheme 1.28 Moore's synthesis of isoarnebifuranone (**1.188**)



Moore and coworkers next expanded the scope of the rearrangement by using alternative squarate electrophiles (Scheme 1.29). Rather than the simple dimethylsquarate (**1.186**), the more complex methyl *t*-butoxy squarate **1.191** was used in the total synthesis of terreic acid (**1.189**). Two syntheses of the naturally occurring antibiotic[87] were reported elsewhere; however, both syntheses required lengthy, low yielding sequences to the natural product.[88,89] Moore and coworkers saw this as a potential application of their methodology with the goal of obtaining the natural product more efficiently. The synthesis of **1.195** began with the reaction of squaric acid (**1.189**) and trimethylorthoformate with *t*-butyl alcohol as the solvent to deliver bis-*t*-butoxy squarate **1.190** in 77% yield.[69] Reaction of one equivalent of MeLi followed by acylation with

TFAA delivered **1.191** in an unrecorded yield. Addition of lithium acetylide (**1.192**) to **1.191** delivered alcohol **1.193** as the only regioisomer in 56% yield. The regioselectivity of the addition is due to the higher electrophilicity of the ketone carbonyl carbon atom rather than the vinylogous ester.[31] Heating **1.193** in PhH under reflux furnished a quinone **1.194** in 79% yield. Quinone **1.194** subsequently underwent epoxidation under basic conditions followed removal of the *t*-butyl protecting group with TFA to deliver the natural product **1.195** in 50% yield across two steps. Interestingly, the racemic mixture of **1.195** was found to be more biologically active than either of the resolved enantiomers.

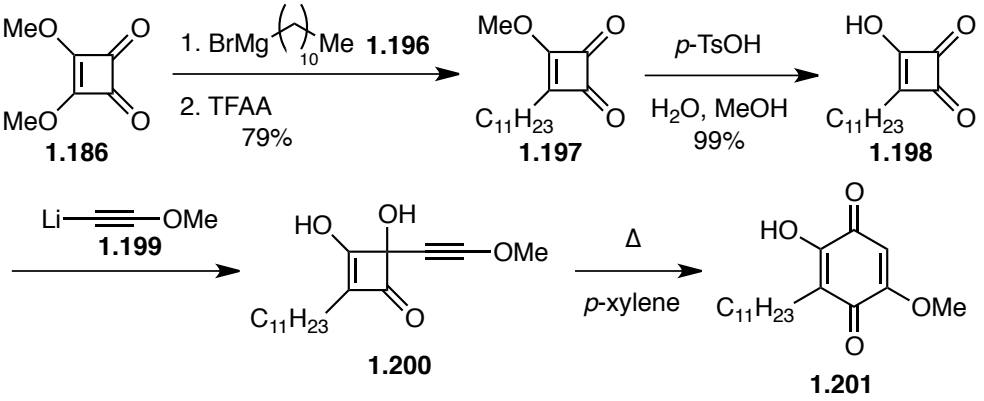
Scheme 1.29 Moore's synthesis of terreic acid



One of the more interesting applications of the Moore rearrangement to total synthesis was with the preparation of quinone 5-*O*-methylembelin (**1.201**) by Miles and coworkers (Scheme 1.30).[90] The natural product was isolated in 1989 by Gomez and coworkers, and it was reported to have antifungal properties as well as toxicity to fish at concentrations as low as 1 ppm.[91] The squarate **1.186** was first allowed to react with undecylmagnesium bromide (**1.196**), followed by dehydration with TFAA to provide the alkylated squarate **1.197** in 79% yield. The methoxy group of **1.197** was hydrolyzed with *p*-TsOH to give squarate **1.198** in quantitative yield. Two equivalents of the lithium acetylide of methoxy acetylene[92] **1.199** were required for the next step in the synthesis.

The first equivalent reacted with the acidic proton of **1.198**, while the second equivalent reacted with the ketone to provide the observed product **1.200**. Due to its unstable nature, **1.200** was subjected to the Moore rearrangement without purification to furnish the natural product **1.201**. Unfortunately, yields for the remaining reactions were not reported, and the author implied the final steps were low yielding.

Scheme 1.30 Miles' synthesis of 5-*O*-methylembelin using the Moore rearrangement

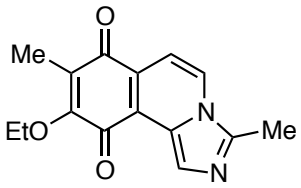


1.5.1 Cribrostatin 6

One last example of using the Moore rearrangement in a total synthesis application was reported by Dr. Daniel Knueppel in his synthesis of cribrostatin 6 (**1.202**).[93,94] Cribrostatin 6 was isolated in 2003 from the marine sponge *Cribrochalina* sp by Pettit and coworkers.[95,96] The quinone natural product was reportedly active against numerous pathogenic fungi and antibiotic resistant Gram-positive bacteria.[96] Additionally, **1.202** is active against human and murine lung cancer cell lines with an ED_{50} of 0.3 μg/mL.[96] To date, total syntheses of cribrostatin 6 have been reported by Nakahara in 18 steps with 0.8% overall yield,[97,98] Kelly in 15 steps in 3.1% overall yield,[99] and Martin.[93,94] Each synthesis has several elegant transformations that provide

access to the natural product; however, the Martin group's Moore rearrangement strategy is by far the most efficient route to the natural product.

Figure 1.5 Structure of the quinone natural product cribrostatin 6 (**1.202**)

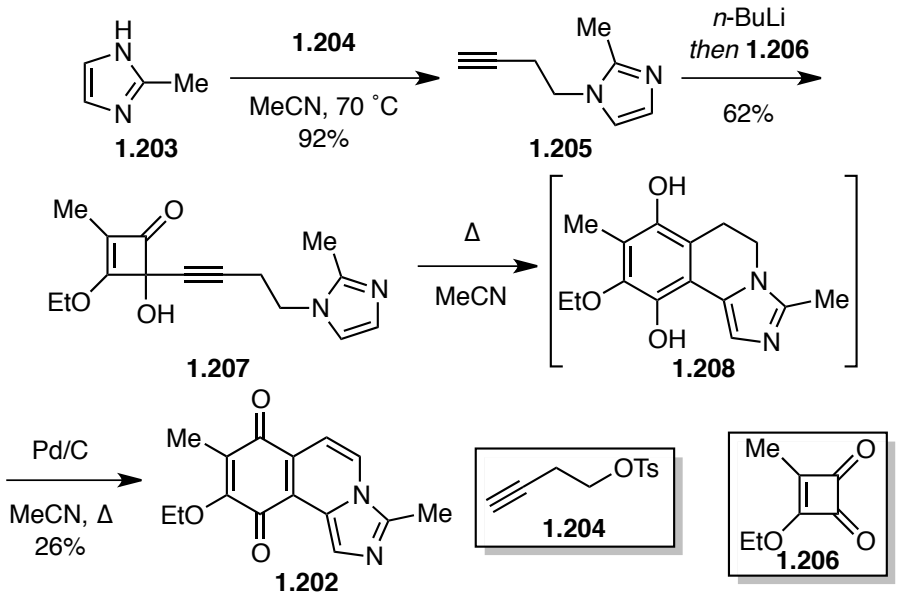


1.202

1.5.1.1 The Martin group's synthesis of cribrostatin 6

Dr. Knueppel saw a potential application of the Moore rearrangement buried within the quinone portion of cribrostatin 6 (**1.202**). The synthesis of the natural product commenced with the reaction of 2-methylimidazole (**1.203**) with tosylate **1.204** to provide the alkylated imidazole **1.205** in 92% yield. The lithium acetylide of **1.205** was formed with *n*-BuLi and then reacted with squarate **1.206**[67] to deliver the alcohol **1.207** in 62% yield. The pivotal Moore rearrangement was next explored. After screening a number of reaction conditions, Dr. Knueppel found that heating **1.207** in MeCN at high dilution (0.001 M) provided an intermediate hydroquinone **1.208** after homolytic aromatic substitution. By stirring a mixture of **1.208** in MeCN in the presence of Pd/C open to ambient oxygen, cribrostatin 6 (**1.202**) was obtained in 26% yield over two steps.

Scheme 1.31 Martin's synthesis of **1.202** using the Moore rearrangement



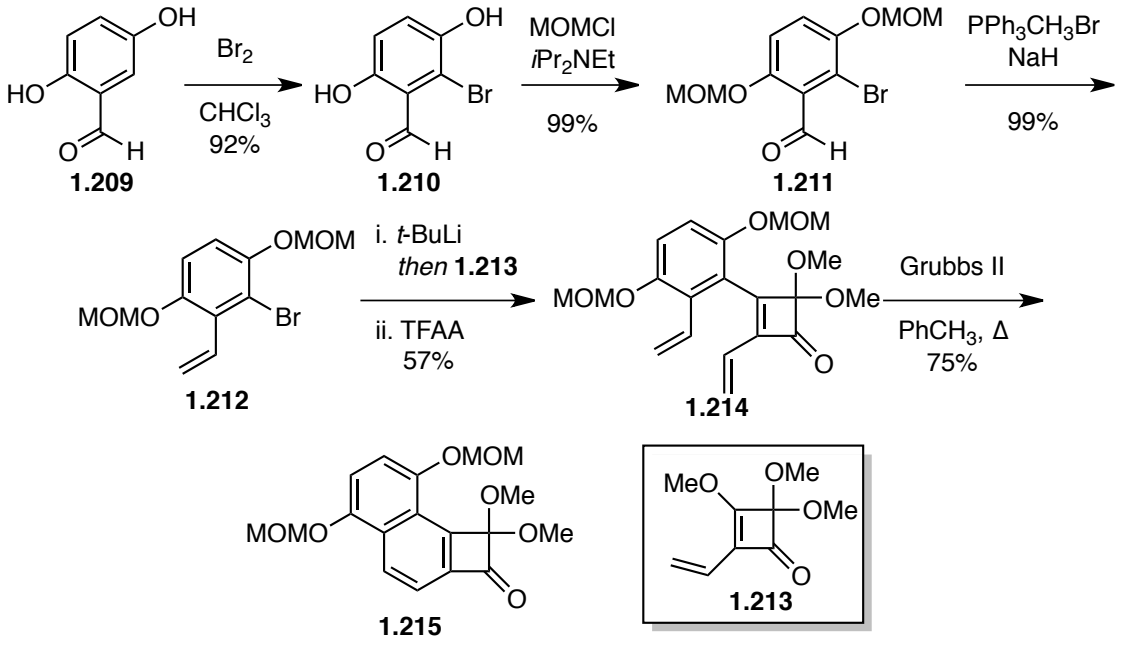
The sequence presented in Scheme 1.31 required five total steps with four in the longest linear sequence. The natural product was obtained in 14% overall yield without the use of protecting groups. The synthesis of the natural product by the Moore rearrangement is more efficient in terms of step count and overall yield. The short route also allowed Dr. Knueppel to prepare several analogs of **1.202** that would have been difficult to prepare using either Nakahara's or Kelly's synthesis.

1.6 Application of the Moore Rearrangement to the Synthesis of IB-00208

The retrosynthesis of IB-00208 shown in Scheme 1.25 has seen several iterations. Although the original retrosynthesis has changed significantly, a key step in each new approach has been a Moore rearrangement to prepare the quinone-xanthone core of the natural product. Dr. Knueppel has recently summarized the previous efforts that he made on the project, and has also proposed several endgame strategies by which the natural product could be obtained.[77] In the following sections, the attempted synthesis of **1.7** by Dr. Knueppel, as well as a proposed endgame, will be discussed.

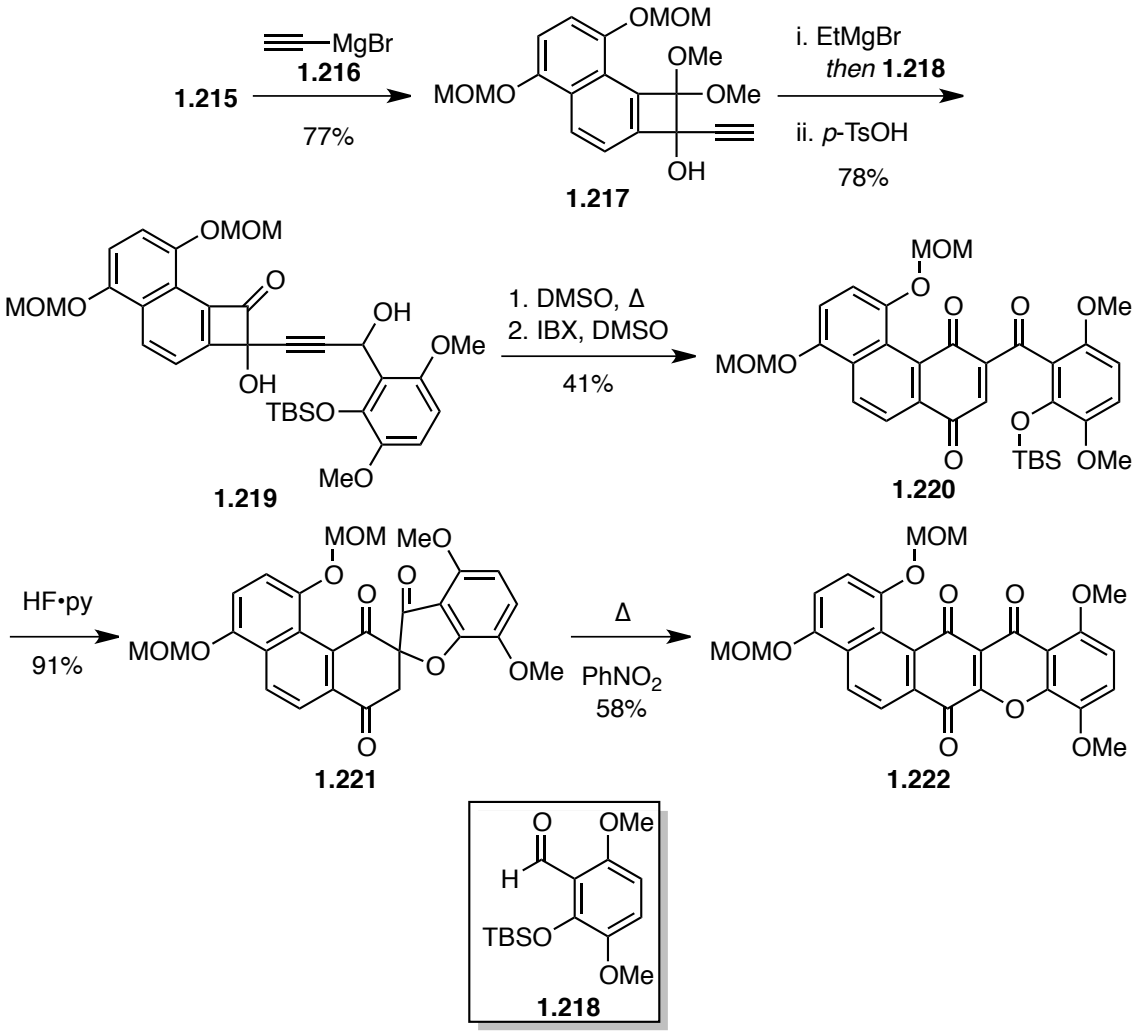
Initial efforts were focused on the preparation of an appropriately substituted squarate derivative that would be used in the Moore rearrangement (Scheme 1.32). Regioselective bromination of 2,4-dihydroxybenzoic acid (**1.209**) took place in 92% yield, delivering **1.210** in 92% yield. Both of the phenolic oxygen atoms were protected as their MOM ethers **1.211** in 99% yield, and the aldehyde moiety was subjected to a Wittig reaction to provide styrene **1.212** in 99% yield. The aryl bromide of **1.212** underwent lithium/halogen exchange with excess *t*-BuLi, followed by reaction with squarate **1.213** and then dehydration with TFAA to provide the ketone **1.214** in 57% yield. The ketone **1.214** was subjected to a ring closing metathesis with Grubbs second-generation ruthenium catalyst to furnish the tricyclic ketone **1.215** in 75% yield. With **1.215** in hand, Dr. Knueppel focused his efforts on preparing the Moore rearrangement precursor.

Scheme 1.32 Synthesis of benzocyclobutanone **1.215**



The carbonyl moiety of **1.215** was treated with ethynyl magnesium bromide (**1.216**) to deliver the unstable propargylic alcohol **1.217** (Scheme 1.33). Exposure of **1.217** to excess ethyl magnesium bromide formed the putative dianion, which was then reacted with aldehyde **1.218** to deliver a diol. The acetal moiety of **1.217** was then hydrolyzed with *p*-TsOH to deliver the ketone **1.219** in 78% overall yield. This sequence required significant optimization, and it was discovered that the magnesium bromide salt of the dianion of **1.217** provided the highest yield and cleanest reaction mixtures. The Moore rearrangement was induced by heating a solution of **1.219** in deoxygenated DMSO from ambient temperature to 120 ˚C. The benzylic alcohol moiety of the resulting product was then oxidized with IBX to the ketone **1.220** in 41% yield across two steps. The phenolic oxygen atom of **1.220** was unmasked with HF•pyridine, which spontaneously cyclized to the spirocycle **1.221** in 91% yield instead of the xanthone. Dr. Knueppel put forth significant effort to prevent the formation of the spirocycle **1.221**, but it was always observed upon removal of the TBS protecting group. Inspired by the rearrangement reported in the work of bikaverin by Giles and coworkers,[47] heating a solution of **1.221** under reflux in $PhNO_2$ delivered the quinone-xanthone **1.222** in 58% yield. The intermediate xanthone formed after rearrangement presumably undergoes oxidation to the quinone moiety with $PhNO_2$ or oxygen acting as the oxidant. An x-ray crystal structure was obtained for pentacycle **1.222**, verifying the quinone-xanthone core was present.

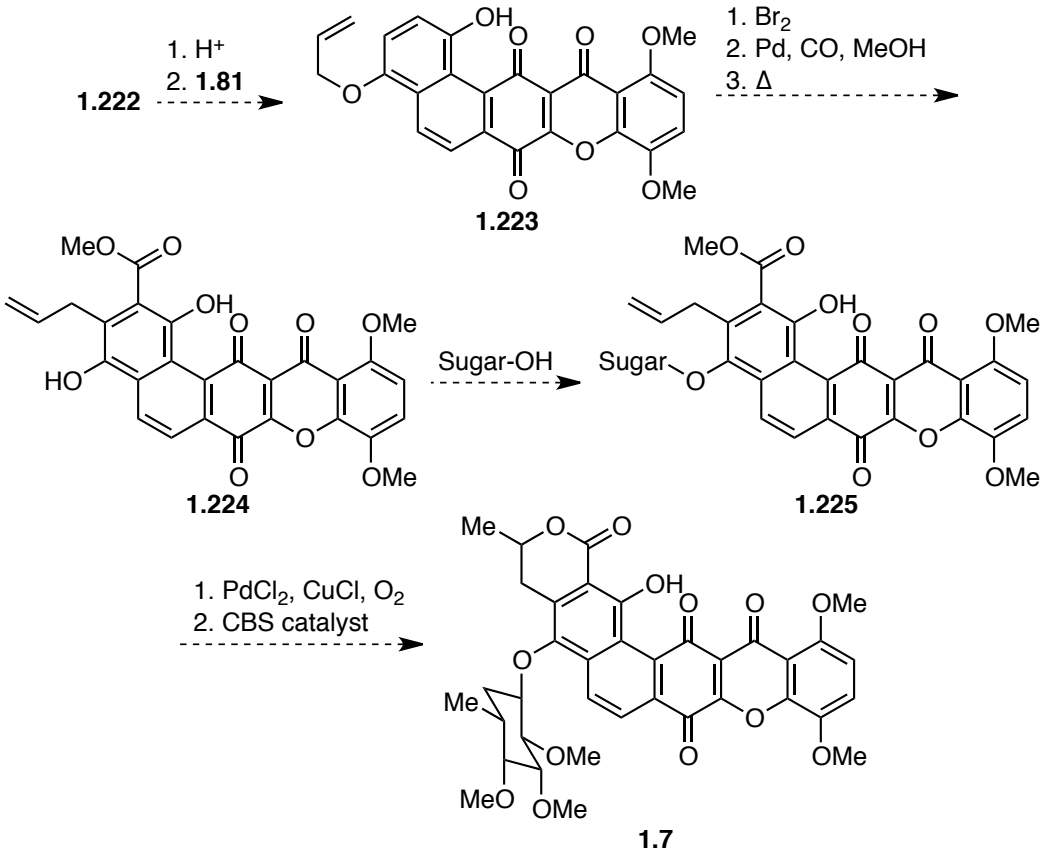
Scheme 1.33 Synthesis of pentacycle **1.222** using the Moore rearrangement



The endgame approach that Dr. Knueppel envisioned is shown in Scheme 1.34. Removal of the MOM-protecting groups of **1.222** under acidic conditions followed by allylation of the more accessible phenolic oxygen atom with **1.81** under Mitsunobu conditions will deliver **1.223**. Bromination of **1.223** *ortho* to the remaining phenol group, carbonylation of the aryl bromide in the presence of MeOH, and then a Claisen rearrangement will provide the aryl ester **1.224**. Dr. Knueppel envisioned the sugar moiety would be regioselectively appended to a phenol, again taking advantage of the

fewer steric interactions around the desired phenolic oxygen. Finally, Wacker oxidation of the allyl group will give a ketone that will then undergo reduction with the CBS catalyst to the alcohol. The resulting alcohol would then spontaneously cyclize to form the lactone A-ring of **1.7**. Since the stereochemistry of the A-ring methyl group of **1.7** is unknown, Dr. Knueppel proposed using both enantiomers of the CBS catalyst to provide both enantiomers of the natural product.

Scheme 1.34 Projected endgame strategy to **1.7**



1.7 Summary and Conclusions

The synthesis of quinone natural products using the Moore rearrangement is a powerful and effective tactic. A successful extension of the Moore rearrangement to the

realm of 1,4-dioxygenated xanthone natural products such as IB-00208 would make it an even more attractive alternative than the methods that are currently available. The reaction has been applied to the synthesis of natural products, and it has allowed facile access to an advanced pentacyclic intermediate in the synthesis of IB-00208 (**1.7**); however, its use in the context of 1,4-dioxygenated xanthone natural products such as those shown in Figure 1.1 has not been reported. The current methods by which 1,4-dioxygenated xanthones have been synthesized oftentimes result in low yielding sequences and unnecessarily high step counts.

A new synthesis of 1,4-dioxygenated xanthone is needed. Ideally, this method would be general and widely applicable to substrates ranging from simple xanthones to complex natural products, tolerant to a diverse set of functional groups, and efficient with minimal steps to obtain the desired product. Within the retrosynthesis of IB-00208, Dr. Douglas Mans proposed a method to the xanthone core of the natural product employing a Moore rearrangement as the key step. We queried whether this proposed reaction could be applied to the preparation of 1,4-dioxygenated xanthones in a more general sense.

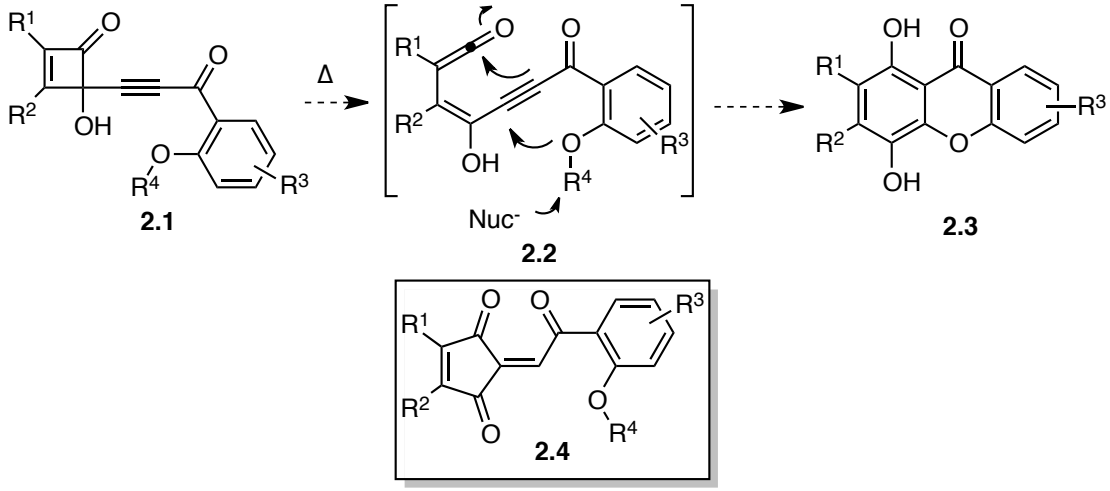
Chapter 2: Application of the Moore Rearrangement to the Synthesis of 1,4-Dioxygenated Xanthones

2.1 A New Synthesis of 1,4-Dioxygenated Xanthones

The goal of the project was to find a new route to 1,4-dioxygenated xanthones using a combination of the Moore rearrangement and a reaction that was reported by Fuganti. We hoped to combine the two methodologies into a general method by which 1,4-dioxygenated xanthones and related natural products could be prepared quickly and efficiently. We recognized the paucity of general approaches to 1,4-dioxygenated xanthones and were confidant that proposing a Moore rearrangement as a key step in the sequence would be an improvement over the prior art by obtaining xanthones in a modular and convergent manner.

The initial approach we developed is shown in Scheme 2.1. We envisioned that thermolysis of an ynone such as **2.1** would induce the ring-opening of the cyclobutenone to the ketene intermediate **2.2**. A nucleophile would then unmask the phenolic oxygen atom, inducing cyclization onto the alkyne with subsequent cyclization onto the ketene to deliver the 1,4-dioxygenated xanthone **2.3** in a one-pot process. There is a possibility to form the five membered cyclopentanedione **2.4** since a carbonyl group is attached to the alkyne (*cf*. Scheme 1.26); however, if cyclization of the aryl oxygen atom occurs prior to the Moore rearrangement, the probability to form the desired xanthone **2.3** would be much greater. Since we were interested in obtaining xanthones quickly, initial efforts were focused on the synthesis of ynones of general structure **2.1**.

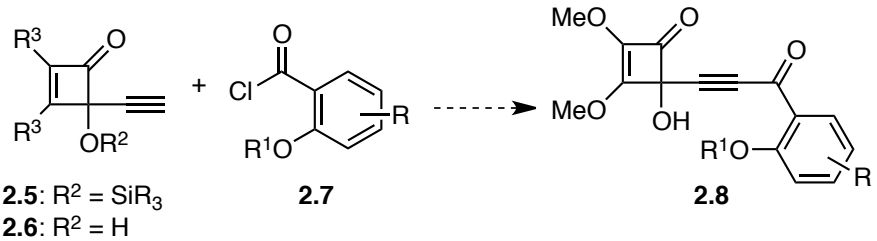
Scheme 2.1 The Martin group's proposed route to 1,4-dioxygenated xanthones



2.1.1 Ynones as xanthone precursors

The approach to ynones of general structure **2.8** that we envisioned is shown in Scheme 2.2. Reaction of the acetylide ion of protected squarate **2.5** with the acid chloride **2.7** would deliver an ynone. The silicon-protecting group of the resulting ynone would then be cleaved upon workup or in a subsequent step. Alternatively, the dianion of **2.6** could be generated with excess base and, after addition of the acid chloride **2.7**, deliver the ynone **2.8** in a one-pot process. Due to the inherent difficulty associated with dianion chemistry, such as sensitivity to moisture and solubility at low temperatures, we began our investigations by first preparing the silicon-protected squarate **2.5**.

Scheme 2.2 Proposed synthesis of ynones



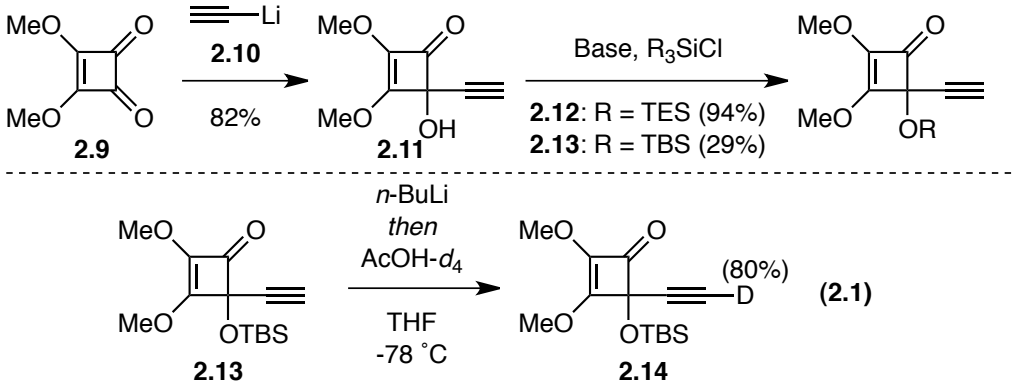
2.5: $R^2 = SiR_3$
2.6: $R^2 = H$

2.7

2.8

The silicon-protected squarates were prepared according to the route shown in Scheme 2.3. Reaction of dimethylsquarate (**2.9**)[70] with lithium acetylide (**2.10**)[100,101] delivered the squarate **2.11** in 82% yield. The alcohol of the squarate was then protected as its triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBS) ethers **2.12** and **2.13** in 94% and 29% yields, respectively. Although the yield of **2.13** was not optimized, it provided us with sufficient material to began exploratory studies toward the ynone. A streamlined process was attempted in which the intermediate alkoxide formed after reaction of **2.9** with **2.10** was quenched with the silyl chloride. Unfortunately, the yield of the protected product was less than 10%. Before we began studying the coupling reaction between the acid chloride and the protected squarates, we queried whether the acetylide of a protected squarate could be generated cleanly. To test this hypothesis, the lithium acetylide of **2.13** was generated with *n*-BuLi and reaction with AcOH-d_4 provided a product with ~80% deuterium incorporation in good yield (Equation 2.1). This gave us confidence that we could cleanly generate the acetylide anion. We next turned to the preparation of the acylating agents.

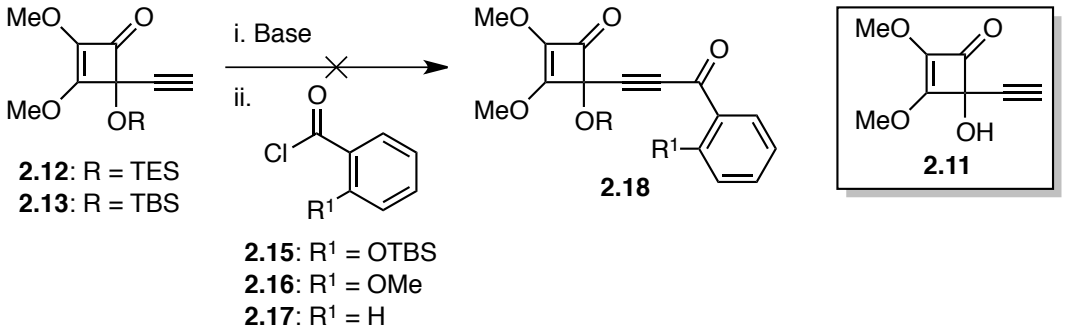
Scheme 2.3 Preparation of protected squarates



The acid chlorides that were used in the studies were the TBS-protected benzoyl chloride **2.15**,[102] anisoyl chloride (**2.16**), and benzoyl chloride (**2.17**).[103] With both

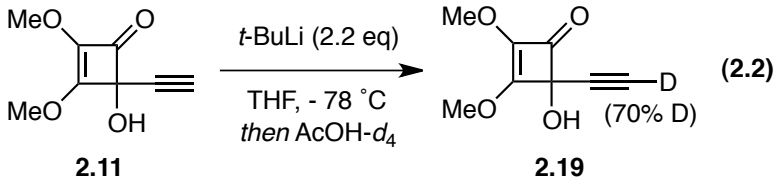
squarate and acid chlorides in hand we began investigating the key coupling (Scheme 2.4). We applied the successful conditions that were used in Equation 2.1 to the reaction between the squarates and acid chlorides. Unfortunately, there was no evidence that an ynone was formed during the reaction. Instead, we obtained the deprotected squarate **2.11** in low yield. After additional unsuccessful attempts, we began screening bases (*n*-BuLi, *t*-BuLi, LDA, LiTMP, LiHMDS, NaH, *t*-BuMgCl, and $NaNH_2$), solvents (THF, Et_2O, DME), and temperatures (-78 ˚C to reflux) only to find no evidence that an ynone was formed. In most cases, the only isolable product from the reaction was the deprotected squarate **2.11**. We queried whether the silicon protecting groups of **2.12** and **2.13** were having an adverse effect on the coupling since **2.11** was oftentimes recovered after the reaction. Accordingly, we began exploring the use of the dianion of **2.6** as the nucleophile.

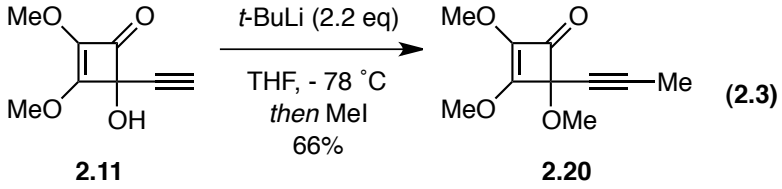
Scheme 2.4 Unsuccessful ynone formation with the acetylide anion



Before attempting the dianion reaction with an acid chloride, the amount of dianion formed in the reaction with base was quantified. Exposing **2.11** to excess *t*-BuLi in THF at -78 ˚C followed by quenching with AcOH-d_4 provided **2.19** with ~70% deuterium incorporation at the alkyne carbon (Equation 2.2). In another test reaction, the dianion of **2.11** was generated and then quenched with excess MeI (Equation 2.3). The bismethylated squarate **2.20** was obtained in ~66% yield. Although the deuterium

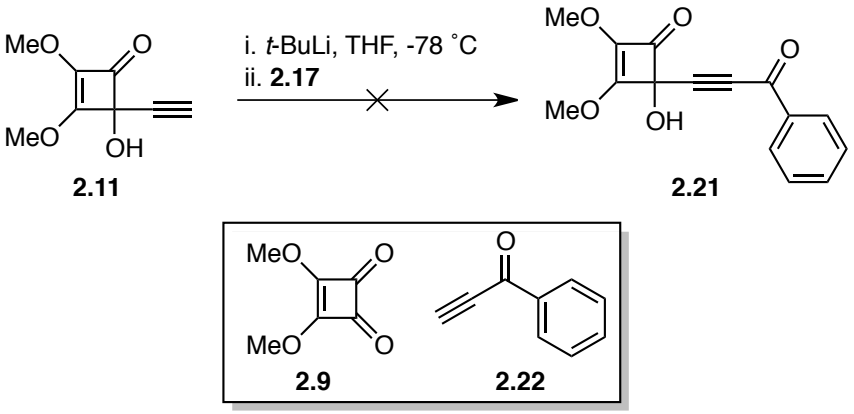
incorporation was not quantitative, we were confident that conditions could be optimized should the dianion reaction prove to be successful.



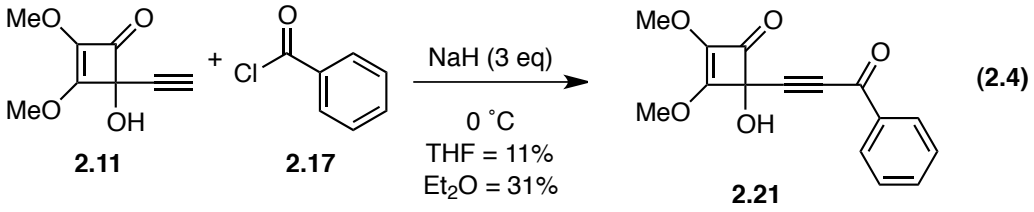


With conditions by which the dianion of **2.11** could be generated, the coupling reactions were next explored. In the event, the dianion of **2.11** was generated according to the conditions in Equation 2.2, but quenching the reaction with **2.17** resulted in no formation of ynone **2.21** (Scheme 2.5). Instead, squarate **2.9** and ynone **2.22** were the only isolable products from the reaction mixture. After screening several bases, solvents, and the remaining electrophiles (**2.15**, **2.16**), we had no evidence suggesting the ynone was formed.

Scheme 2.5 Unsuccessful ynone formation with dianion chemistry



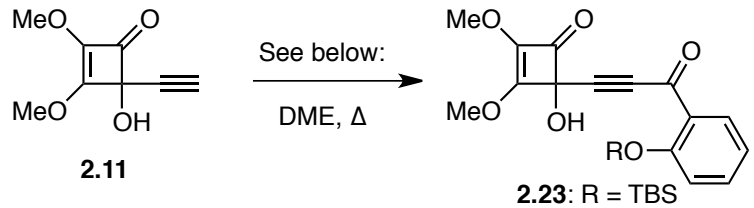
A significant amount of effort was expended toward obtaining the ynone *via* the reaction shown in the preceding scheme. Mixed base systems, slow addition of reagents, and inverse addition of reagents were some of the complex modifications that were tried. After a large number of failures, we decided to take a different approach to the dianion reaction, namely by adding a base to a pre-mixed solution of the alkyne and the acid chloride. Stirring a mixture of **2.11** and **2.17** with NaH in THF at 0 ˚C delivered the ynone **2.21** in 11% yield (Equation 2.4). Running the identical reaction in the less coordinating solvent Et_2O furnished the ynone **2.21** in 31% yield. The operationally simple reaction conditions were applied to the remaining electrophiles.



(2.4)

After optimization of the solvent, equivalents and reaction time, we discovered that the ynones could be prepared in synthetically useful yields (Table 2.1). Using **2.15** as the electrophile (Entries 1 and 2), we obtained a 99% or 73% yield of **2.23** using NaH or KH, respectively. Switching to anisoyl chloride (**2.16**) as the electrophile led to a 64% or 29% yield of **2.24** when either NaH or KH, respectively, were used (Entries 3 and 4). In order to drive the reaction to completion, a high boiling ethereal solvent was required. Heating the reaction in Et_2O or THF required long reaction times, but use of dimethoxyethane (DME) as solvent shortened the reaction time significantly. This enabled us to prepare the ynones on sufficient scale to continue with the synthesis.

Table 2.1 Successful ynone formation with hydride bases

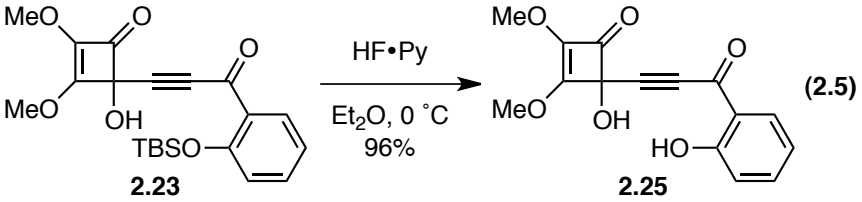


2.11

2.23: R = TBS
2.24: R = Me

Entry	Electrophile	Base (3 eq)	Yield of ynone (%)
1	**2.15** (TBS)	NaH	99
2	**2.15** (TBS)	KH	73
3	**2.16** (Me)	NaH	64
4	**2.16** (Me)	KH	29

A third ynone was obtained by treating **2.23** with HF•pyridine to provide the phenol ynone **2.25** in 96% yield (Equation 2.5). With ynones **2.23**, **2.24**, and **2.25** in hand, studies were next directed toward the cyclization sequence.

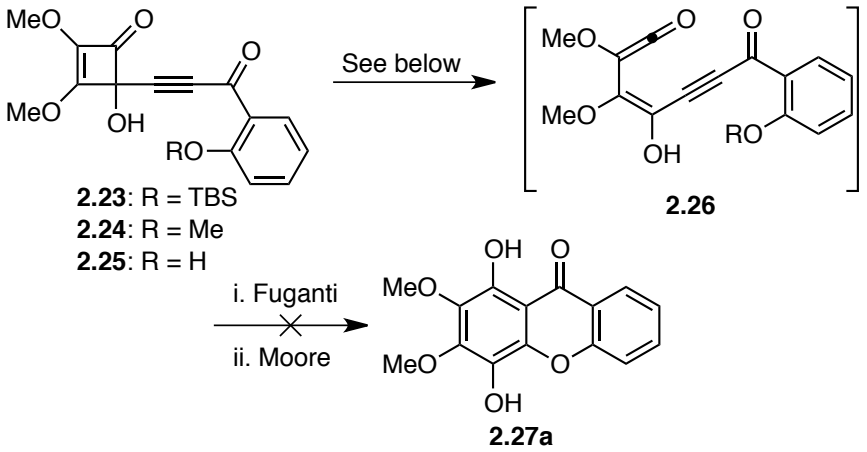


2.23 **2.25** **(2.5)**

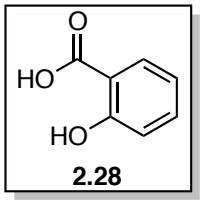
In the desired sequence of cyclizations, we envisioned that the squarate portion of an ynone would undergo the 4π-electrocyclic cyclobutene ring opening to give an intermediate ketene of general structure **2.26**. By the action of an exogenous nucleophile, cyclization of the phenoxide would commence onto the alkyne, which would then cyclize onto the ketene to give the xanthone **2.27a**. Unfortunately, after an extensive screening of nucleophiles and reaction conditions, the xanthone was never observed in the reaction (Table 2.2). In Entries 1-3, exposure of **2.23** to a fluoride source did not promote the cyclization of the phenoxide. Instead, we obtained cleavage of the O-TBS bond and isolated **2.28** after the reaction. The formation of **2.28** could arise from the presence of adventitious H_2O in the reaction. Removing methyl groups from phenolic oxygen atoms

requires harsh reagents and forcing reaction conditions. Each reagent in Entries 4-6 is known to deprotect aryl methyl ethers.[104] Unfortunately, they proved too harsh for the deprotection and cyclization, with many reactions forming intractable mixtures of products. A commonly isolated side product was **2.29**, which presumably forms by the attack of H_2O onto the ynone carbonyl, followed by collapse of the tetrahedral intermediate with loss of the acetylide anion of **2.11**. We next tried the cyclization on the free phenol **2.25** under neutral (Entry 7), basic (Entry 8), and acidic (Entry 9) reaction conditions. In one case a compound with spectral data consistent with the flavone **2.31** was isolated, but the reaction was not reproducible and we elected not to pursue the screening further. In view of the disappointing results shown in Table 2.2, we realized that the Moore rearrangement on the ynone system was going to be a significant challenge, so we decided to alter our strategy.

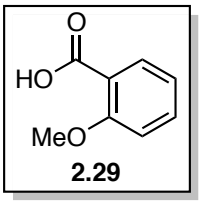
Table 2.2 Unsuccessful preparation of xanthones from ynones



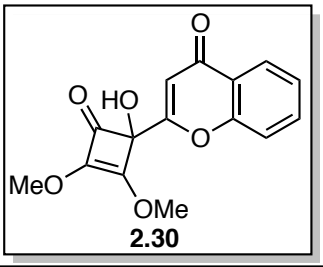
Entry	**2.23**: R = TBS	Entry	**2.24**: R = Me	Entry	**2.25**: R = H
1	TBAF, $PhCH_3$, Δ	4	LiCl, DMF, Δ	7	Δ in misc. solvents
2	TBAF, DMF, rt	5	$CeCl_3$, NaI, MeCN, Δ	8	K_2CO_3, acetone, Δ
3	KF, 18-Cr-6, DMF	6	NaCN, DMSO, Δ	9	*p*-TsOH, CH_2Cl_2, Δ



2.28



2.29



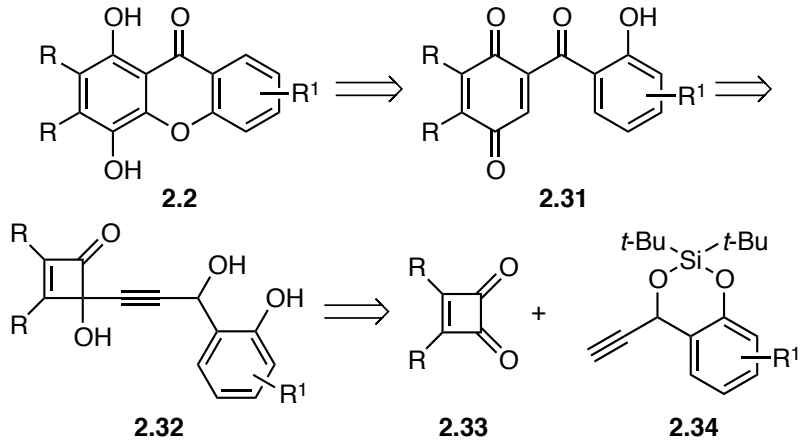
2.30

2.2 USE OF A SILICON-TETHERED ALKYNE NUCLEOPHILE

Concurrent with our studies of the ynone cyclizations, we were actively searching for another route to 1,4-dioxygenated xanthones using solely the Moore rearrangement. The results in Table 2.2 should not be that surprising in light of the fact that the Moore rearrangement with alkynyl ketones results in a mixture of the quinone and the five-membered cyclopentanedione with the latter as the major product (*cf*. Scheme 1.26). We did not observe any five-membered ring products after the reaction, but this does not completely rule out the possibility. We decided to use a protected propargylic alcohol since they have been reported to undergo the Moore rearrangement to the quinone with

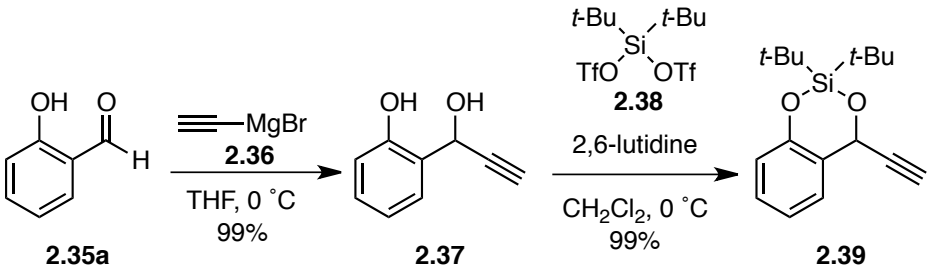
no detectable five-membered ring byproduct (Scheme 2.6).[84] The switch from using an ynone to a protected benzylic alcohol did not drastically change the approach we initially envisioned. The 1,4-dioxygenated xanthone **2.3** would arise from the intramolecular conjugate addition of the phenolic hydroxyl group of keto-quinone **2.31**. Keto-quinone **2.31** is the product of the Moore rearrangement of the diol **2.32** after oxidation of the benzylic alcohol to the ketone. We envisioned the cyclobutenone being derived from the reaction of the acetylide anion of a suitably protected propargyl alcohol such as **2.34** with the generalized squarate **2.33**. Notably, the benzylic alcohol and the phenol are protected using a silicon-tethered protecting group that was discovered by Corey and Trost.[105,106] Like the TBS group, the tether can be removed under very mild conditions in high yields.

Scheme 2.6 Retrosynthesis of xanthones using a silicon tethered protecting group



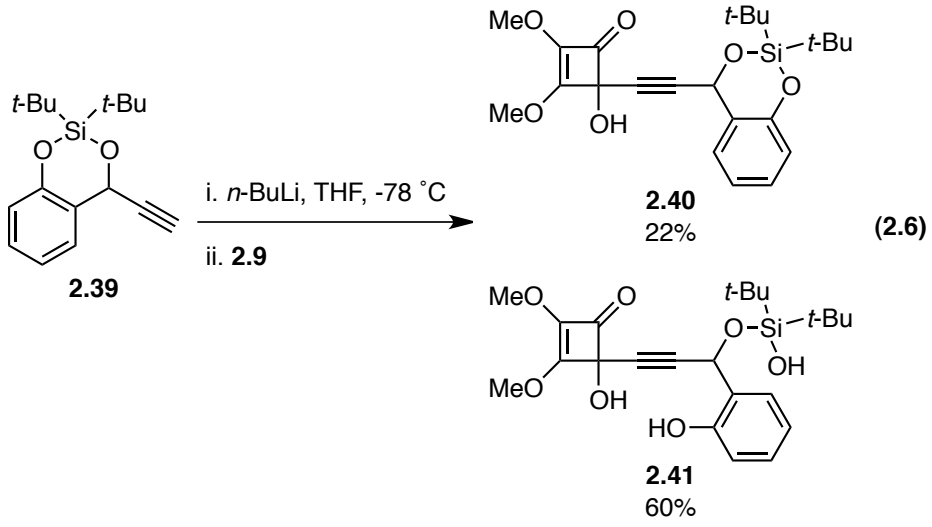
Salicylaldehyde (**2.35a**) was chosen as the initial substrate to undergo the reactions in the preceding scheme because it was readily available (Scheme 2.7). Exposure of **2.35a** to excess ethynyl magnesium bromide (**2.36**) delivered **2.37** in quantitative yield. Stirring a mixture of **2.37** and **2.38** in the presence of 2,6-lutidine furnished **2.39** in quantitative yield. Both of the reactions in Scheme 2.7 required only filtration through a short plug of silica gel to afford analytically pure products.

Scheme 2.7 Ethynylation and protection of salicylaldehyde **2.35a**



2.35a **2.37** **2.39**

The next step in the sequence was the reaction of the alkyne **2.39** with the squarate (Equation 2.6). In the event, formation of the acetylide anion of **2.39** with *n*-BuLi occurred at -78 ˚C, and reaction of this anion with **2.9** resulted in a mixture of the desired product **2.40** in 22% yield and the hydrolyzed product **2.41** in 60% yield.



2.39

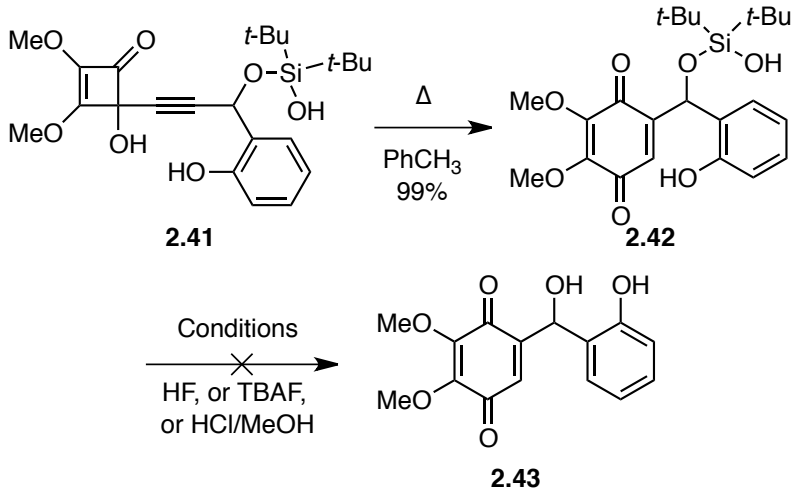
2.40 22%

2.41 60%

(2.6)

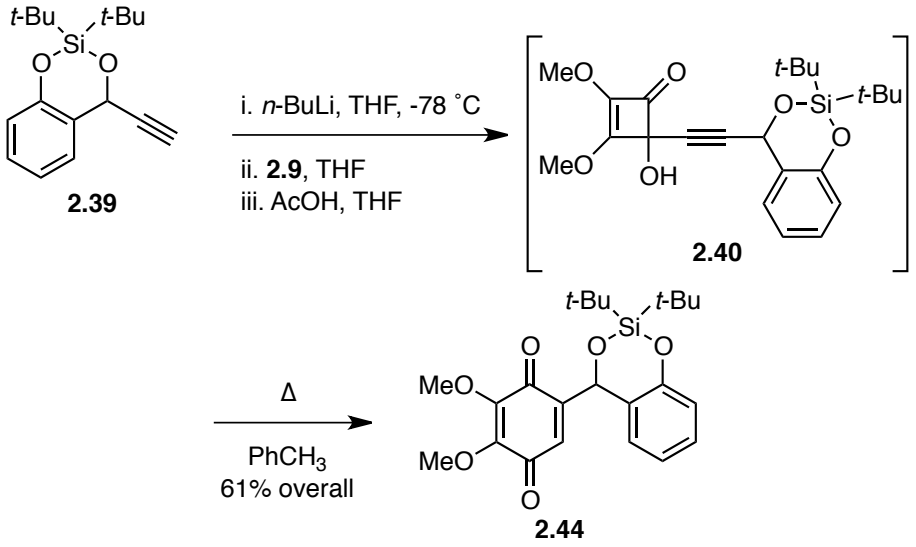
Since silanol **2.41** was obtained in good yield, it was subjected to the conditions of the Moore rearrangement (Scheme 2.8). Heating **2.41** in $PhCH_3$ delivered the quinone **2.42** in quantitative yield. Unfortunately, removal of the protecting group using HF•pyridine, TBAF/AcOH, or HCl/MeOH was unsuccessful, and **2.42** was recovered. Efforts were then turned towards preventing the formation of the silanol side product.

Scheme 2.8 Unsuccessful elaboration of the silanol to a xanthone



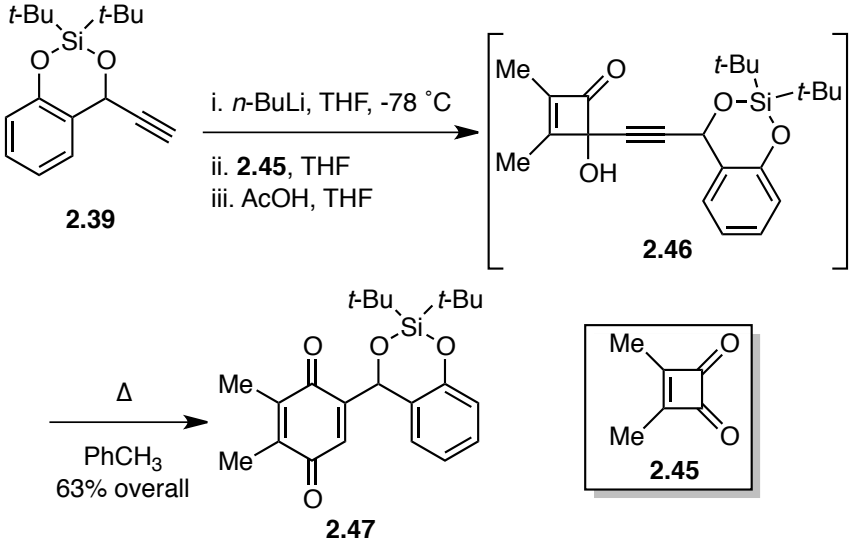
If the hydrolysis side product **2.41** was formed in the presence of water, then excluding water from workup of the reaction should preclude its formation. In the event, quenching the acetylide addition of **2.39** to **2.10** with anhydrous AcOH, concentrating the reaction to remove solvent, and removing the salts by vacuum filtration afforded the desired addition product **2.40** (Scheme 2.19). This material was not purified, but was heated to initiate the Moore rearrangement to give quinone **2.44** in 61% overall yield. The entire sequence was thus streamlined, and none of the silanol **2.41** was detected in the crude reaction mixture. Performing the Moore rearrangement in the microwave oven does lead to higher yields and requires shorter times, but the reactions can only be performed on small scales. Conventional heating is more practical as it is amenable to large-scale reactions (>1 g).

Scheme 2.9 Preclusion of silanol formation by anhydrous workup



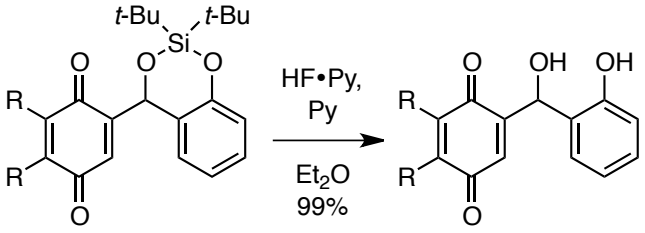
At this time, we queried if another squarate would behave similarly to **2.9** (Scheme 2.10).[30] The squarate **2.45** readily underwent the addition with the acetylide anion of **2.39** followed by the Moore rearrangement to give the quinone **2.47** in 63% overall yield.

Scheme 2.10 Successful utilization of a second squarate



The silicon protecting groups of **2.44** and **2.47**were removed with HF•pyridine to furnish **2.43** and **2.48**in quantitative yield (Scheme 2.11). The deprotection yielded analytically pure material, and the products were taken on to the final oxidation and cyclization steps of the sequence without purification.

Scheme 2.11 Deprotection of the silicon protecting group



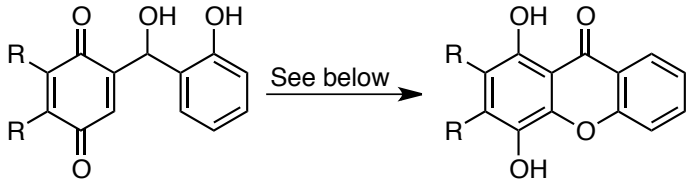
2.44: R = OMe
2.47: R = Me

2.43: R = OMe
2.48: R = Me

The oxidation of the alcohol group in **2.43** and **2.48** to the ketone and subsequent cyclization to the 1,4-dioxygenated xanthone was problematic (Table 2.3). An extensive screening of oxidants was performed for both **2.43** and **2.48**, but the majority of the reagents resulted in intractable mixtures of products. Other oxidants that were tried included MnO_2,[107] $BaMnO_4$,[108,109] Dess-Martin periodinane,[39] IBX,[110] PCC,[111] PDC,[112] TPAP/NMO,[113] TEMPO/$PhI(OAc)_2$,[114] SO_3•pyridine,[115] DDQ,[116] CAN/$NaBrO_3$,[117] oxalyl chloride/DMSO,[118] *N*-bromoacetamide,[119] Ag_2CO_3/Celite,[120] DMSO/P_2O_5,[121,122] CrO_3/pyridine,[123] etc. Gratifyingly, some conditions did generate small amounts of the xanthone. For example, in Entry 1, a chromic acid oxidation led to the desired xanthone **2.27a** in 67% yield, but the reaction was not reproducible. IBX (Entry 2) as an oxidant delivered xanthone **2.27a** in 30% yield, while PDC (Entry 3) generated **2.27a** in only 23% yield. Switching to the methylated analog **2.48** gave similar results. Chromic acid[124] delivered the xanthone **2.49** in 57% yield (Entry 4). Attempts to reproduce the high yield with the same reagent were again unsuccessful. Using IBX (Entries 5 and 6)

provided **2.49** in a 38% or 24% yield seemingly dependent on the presence of DMSO in the reaction. IBX is sparingly soluble in organic solvents except DMSO; thus the higher yield in Entry 5 could be attributed to a higher solubility of the oxidant. Using other oxidants, such as the ones listed above, failed to improve the yield of this sequence.

Table 2.3 Oxidation and cyclization to the 1,4-dioxygenated xanthone



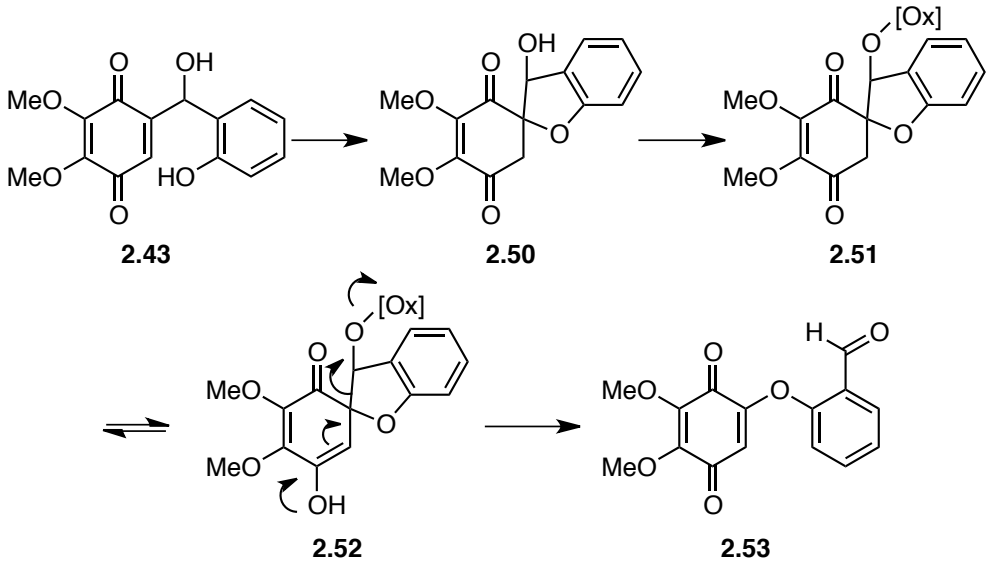
2.43: R = OMe
2.48: R = Me

2.27a: R = OMe
2.49: R = Me

Entry	R	Conditions	Yield of Xanthone (%)
1	OMe	CrO_3, H_2SO_4, H_2O	67, 27
2	OMe	IBX, DMSO, THF	30
3	OMe	PDC, CH_2Cl_2	23
4	Me	CrO_3, H_2SO_4, H_2O	57, 12
5	Me	IBX, DMSO, THF	38
6	Me	IBX, THF	24

The oxidation of **2.43** often led to complex mixtures of products. One of the products commonly isolated from the attempted oxidation of **2.43** was the aldehyde **2.53** (Scheme 2.12), and a mechanism that accounts for its formation has been proposed. The phenolic hydroxyl group of **2.43** presumably cyclizes onto the quinone to form the spirocycle **2.50**, and the benzylic alcohol moiety is then activated by an oxaphilic Lewis acid to give **2.51**. Formation of the keto/enol tautomer **2.52** would then lead to cleavage of the C-C bond with displacement of the oxidant in a retro-aldol type process to deliver the aldehyde **2.53**. An E1cB pathway from the keto tautomer **2.52** is another possibility. Notably, the aldehyde was formed in the presence of strongly oxaphilic oxidants such as PDC, PCC, and chromic acid.

Scheme 2.12 Proposed mechanism of aldehyde formation

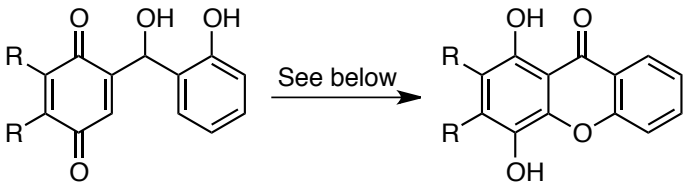


Several oxidants that were investigated for the oxidation and cyclization sequence gave intractable mixtures of products. In the majority of cases, the starting material was consumed but nothing resembling the product was seen in the crude reaction mixture. The Oppenauer oxidation is reported to be tolerant to sensitive functional groups and can successfully oxidize substrates under relatively mild conditions.[104] Preliminary investigations toward applying the Oppenauer conditions to the oxidation and cyclization sequence of **2.43** began with aluminum isopropoxide as the catalyst and cyclohexanone as the sacrificial ketone (Entry 1); however, none of the desired xanthone **2.27a** was isolated from the reaction (Table 2.4). The ketone was then changed from cyclohexanone to benzoquinone[125] due to its higher oxidation potential, but the xanthone **2.27a** was not formed, and **2.54** was isolated. The side product **2.54** presumably arises by the coordination of a second molecule of the starting material with the aluminum species followed by intermolecular hydride transfer, but an intramolecular hydride delivery from the alcohol to the quinone is also possible. This proposed mechanism is tentative at best because there were no other side products isolated from the reactions. Increasing the

equivalents of benzoquinone from 20 to 50 (Entry 2) did not prevent the formation **2.54** during the reaction. Temperature can also have a significant effect on the Oppenauer oxidation, but varying the temperature from 25 ˚C to 120 ˚C had no effect and the hydroquinone was still isolated (Entry 2). In Entry 3, the sacrificial ketone was switched to *m*-nitrobenzaldehyde[126] because it has been shown to be a superior oxidizing agent that allows reactions to be performed at room temperature, but the hydroquinone **2.54** was again the only isolable product.

Applying the Oppenauer oxidation to the dimethyl-substituted quinone **2.48** was actually successful (Entry 4), and delivered the xanthone **2.49** in <27% yield. Performing the oxidation in refluxing $PhCH_3$ (Entry 5) provided the xanthone in 38% yield, but unfortunately hydroquinone **2.55** was formed in an equal amount. Lastly, switching the ketone to *N*-methyl-4-piperidone[127], a ketone that is known to undergo facile reduction under Oppenauer conditions, produced a roughly equivalent amount of **2.49** and **2.55** (Entry 6).

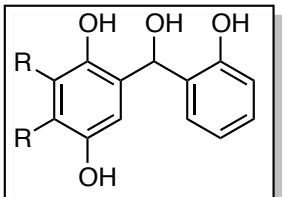
Table 2.4 Application of the Oppenauer reaction to form xanthones



2.43: R = OMe
2.48: R = Me

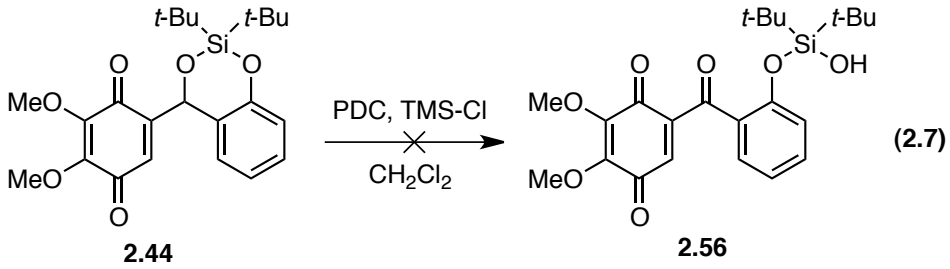
2.27a: R = OMe
2.49: R = Me

Entry	R	Conditions (with $Al(OiPr)_3$)	Solvent, T	Result
1	OMe	Cyclohexanone	PhH, Δ	dec + **2.54**
2	OMe	Benzoquinone (20 - 50 eq)	PhH, rt - Δ	dec + **2.54**
3	OMe	*m*-nitrobenzaldehyde	$PhCH_3$, rt	dec + **2.54**
4	Me	Benzoquinone	$PhCH_3$, 60 ˚C	<27% **2.49**
5	Me	Benzoquinone	$PhCH_3$, Δ	38% **2.49** + 38% **2.55**
6	Me	*N*-methyl-4-piperidone	$PhCH_3$, Δ	18% **2.49** + 13% **2.55**



2.54: R = OMe
2.55: R = Me

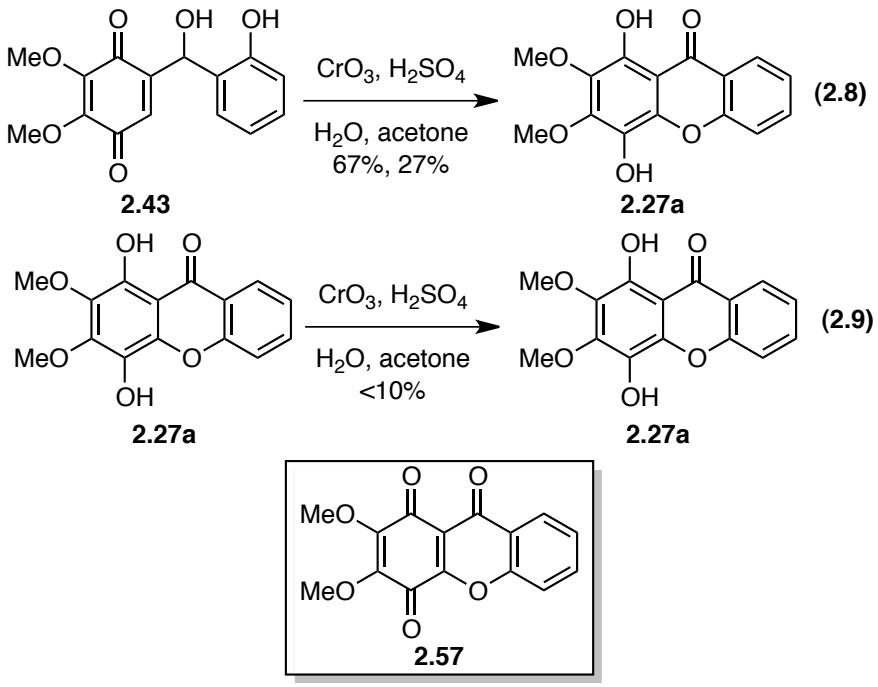
Another attempt to effect the selective oxidation of the benzylic alcohol over the phenol employed chemistry reported by Palomo (Equation 2.7).[128] They reported that secondary TBS ethers could be sequentially deprotected to the alcohol and then oxidized to the ketone in a one-pot process using a mixture of PDC and TMS-Cl. Exposing the protected quinone **2.44** to these conditions resulted in the complete recovery of the starting material and none of the desired ketone **2.56**. The bulky nature of the protecting group could have prevented the deprotection and oxidation sequence.



2.44 **2.56** **(2.7)**

Considering all the setbacks associated with removing the silicon-protecting group, we returned to the oxidation of the unprotected alcohol. It was surprising that the yields of the oxidation and cyclization of **2.43** were not reproducible (Equation 2.8). At the time, we believed the problematic portion of the sequence was the oxidation of the alcohol to the ketone and not the cyclization to xanthone. Our working hypothesis was that any activation of the alcohol could lead to the formation of a very reactive quinone methide that could participate in undesired side reactions. This could be the source of the reproducibility problem, but what we failed to consider was the stability of the product to the reaction conditions.

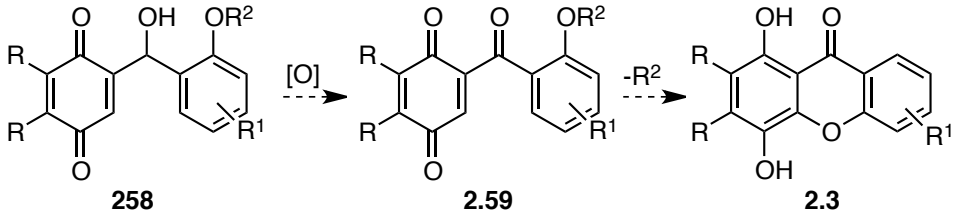
Indeed we found that exposing the xanthone **2.27a** to chromic acid provided less than 10% of recovered starting material, and a significant amount of degradation products were formed (Equation 2.9). There was no evidence that the quinone xanthone **2.57** was formed. After this result was obtained, a new plan was developed in which the oxidation of the alcohol and cyclization to the xanthone would be performed in two separate operations. In other words, the hydroxy xanthone moiety would never be in the presence of an oxidant.



2.3 A REVISED ROUTE TO XANTHONES BY PHENOL PROTECTION

We thus designed a new route to 1,4-dioxygenated xanthones that is shown in Scheme 2.13. We envisioned that the quinone **2.58** would be obtained after the Moore rearrangement of an appropriate squarate. The benzylic alcohol moiety of **2.58** would then be oxidized to the keto-quinone **2.59**. Since we were avoiding the hydroxy xanthone being in the presence of an oxidant, the deprotection of the phenolic oxygen atom would be performed after oxidation of the alcoholic moiety to the ketone to deliver the 1,4-dioxygenated xanthone **2.3** after cyclization. Based on the work that Dr. Knueppel had performed on the synthesis of IB-00208, we decided to protect the phenolic moiety of **2.58** as its methoxymethyl (MOM) ether. The MOM group is capable of surviving basic, mildly acid, oxidative and thermolytic reaction conditions.[129] Thus it is well suited for the proposed sequence to xanthones.

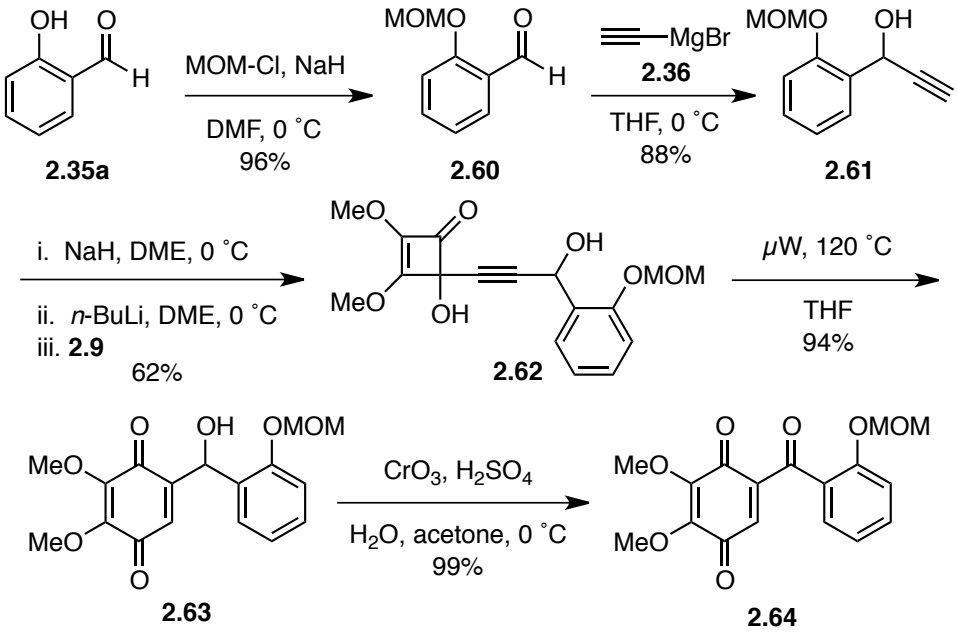
Scheme 2.13 Differential protecting group strategy for the phenol



2.3.1 Use of a MOM Protecting Group

The incorporation of the MOM protecting group on the phenol of salicylaldehyde (**2.45a**) is shown in Scheme 2.14. The phenolic hydroxyl group of **2.45a** was protected with MOM-Cl under basic conditions to give **2.60**, which was then treated with ethynyl magnesium bromide (**2.36**) to give propargyl alcohol **2.61** in 88% yield. The dianion of **2.61**, which was generated using a mixed base procedure of NaH and *n*-BuLi, was treated with **2.9**, and diol **2.62** was isolated in 62% yield. Diol **2.62** underwent the Moore rearrangement upon heating in the microwave oven at 120 ˚C, to deliver quinone **2.63** in 94% yield. The benzylic alcohol of **2.63** was oxidized using chromic acid to the ketone **2.64** in quantitative yield. Other oxidants such as PCC and PDC required longer reaction times and gave poorer yields of the ketone.

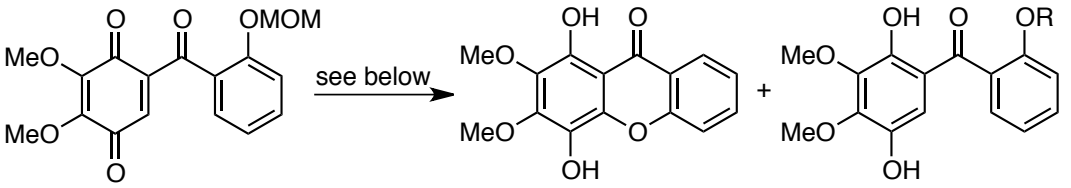
Scheme 2.14 Synthesis of the MOM-protected keto-quinone



All that remained in order to access the desired 1,4-dioxygenated xanthone **2.27a** from keto-quinone **2.64** was removal of the protecting group followed by 1,4-addition of the resulting phenol (Table 2.5). Initial attempts to remove the MOM group included treatment of **2.64** with gaseous HCl in MeCN and concentrated H_2SO_4 in dioxane (Entries 1 and 2). Unfortunately, an inseparable mixture of products was obtained from both reactions. The xanthone **2.27a** as well as several side products were isolated as inseparable mixtures in 81% and 16% yield, respectively. Using concentrated H_2SO_4 (Entry 3) resulted in the formation of the xanthone **2.27a** and hydroquinones **2.65** and **2.66**. It is peculiar that the quinone was reduced to the hydroquinone in the absence of a reducing agent. The hydride-accepting reagent Ph_3CBF_4 was successful in delivering the xanthone without the formation of the hydroquinones, but the yield was 24% (Entry 4). Lastly, TMSI and I_2 in MeOH were employed (Entries 5 and 6), but xanthone **2.27a** and the hydroquinones were formed in roughly equal amounts. Since the removal of the

MOM group was problematic due to the large number of side products, we decided to change protecting groups.

Table 2.5 Deprotection and cyclization of MOM-protected phenol



2.64 **2.27a** **2.65**: R = MOM **2.66**: R = H

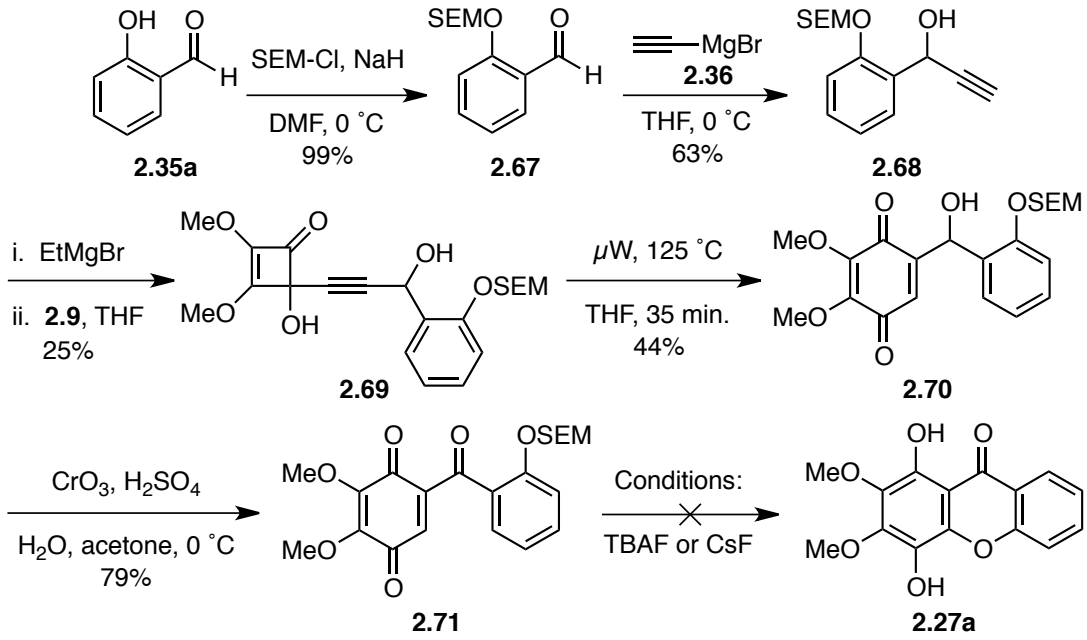
Entry	Conditions	Ratio of **2.27a** : **2.65**+**2.66** (^{1}H NMR)		% yield (of mixture)
1	$HCl_{(g)}$, MeCN	2	--	81
2	H_2SO_4, dioxane	1	--	16
3	H_2SO_4, conc.	1	5	69
4	CPh_3BF_4, CH_2Cl_2	1	--	24
5	TMSI, CH_2Cl_2	1	1	42
6	I_2, MeOH	5	4	44

2.3.2 Use of a SEM Protecting Group

The SEM protecting group has similarities to that of the MOM group in that it is stable to basic reaction conditions and elevated temperatures. It has the added benefit, however, of being readily removed using traditional fluoride sources such as TBAF and CsF (Scheme 2.17).[130] Salicylaldehyde (**2.35a**) was stirred with freshly prepared SEM-Cl under basic conditions to deliver **2.67** in quantitative yield, and the resulting aldehyde was ethynylated to provide propargyl alcohol **2.68** in 63% yield. The dianion of **2.68**, which was generated with excess ethyl magnesium bromide, was allowed to react with **2.9**, and the resulting diol **2.69** was obtained in an unoptimized 25% yield. The Moore rearrangement of **2.69** in the microwave oven at 125 °C provided the quinone **2.70** in 44% yield, and the benzyl alcohol of quinone **2.70** was oxidized to the ketone **2.71** in 79% yield. Having sufficient material for two reactions, exposure of **2.71** to either acetic

acid buffered TBAF or CsF resulted in complex mixtures of unidentified products. None of the desired xanthone **2.27a** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. It is known that methoxy substituted quinones can undergo addition and elimination side reactions under basic conditions, and this could have been a competing background reaction.[131] Unfortunately, we do not have evidence that this addition/elimination reaction was occurring. Concurrent with these investigations, we were exploring a third potential protecting group.

Scheme 2.15 Unsuccessful xanthone preparation with a SEM protecting group

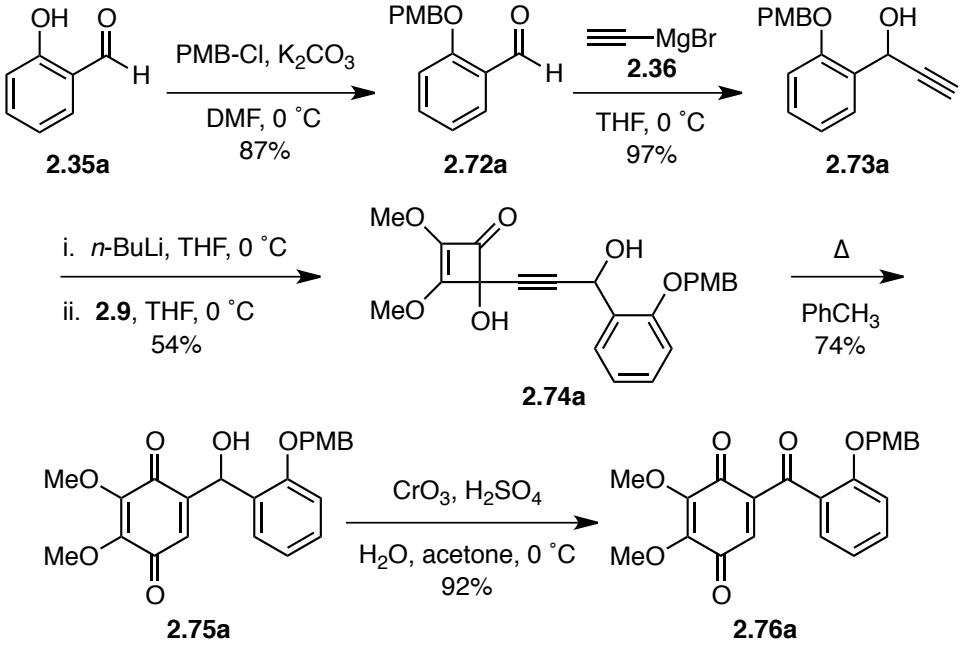


2.3.3 Use of a PMB Protecting Group

The *p*-methoxybenzyl (PMB) group was next investigated as the phenol-protecting group (Scheme 2.16). Like the MOM group, the PMB group is stable to strongly basic conditions; however, the PMB[132] group can be cleaved under acidic and oxidative conditions. For example, reagents such as DDQ and CAN readily cleave the PMB group.[104] Accordingly, the PMB group was installed on salicylaldehyde (**2.35a**) in

87% yield under basic conditions, and the aldehyde **2.72a** was ethynylated to the alcohol **2.73a** in 97% yield. The dianion of **2.73a**, which was generated with 2.2 equivalents of *n*-BuLi, was treated with squarate **2.9** to furnish diol **2.74a** in 54% yield. The Moore rearrangement was performed by conventional thermolysis at 120 ˚C, and quinone **2.75a** was obtained in 74% yield. The alcohol moiety of **2.75a** was oxidized to the ketone **2.76a** using chromic acid in 92% yield. With the keto-quinone **2.76a** in hand, we investigated the one-pot deprotection and cyclization sequence.

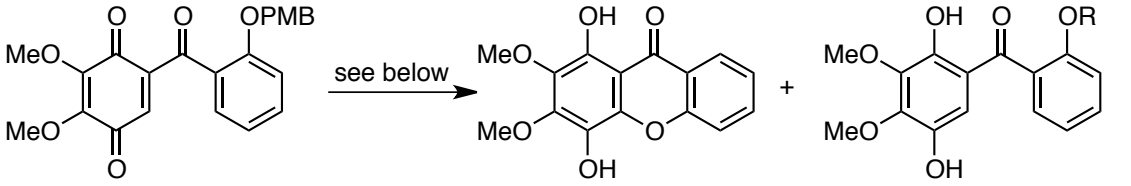
Scheme 2.16 Keto-quinone preparation with PMB protecting group



Use of oxidative reagents that are known to remove the PMB group, such as DDQ and CAN, only resulted in the quantitative recovery of starting material (Entries 1 and 2, Table 2.6). When the hydride acceptor Ph_3CBF_4 (Entry 3) was used, an inseparable mixture (2:1) of the xanthone **2.27a** and hydroquinones **2.66** and **2.77** were obtained. Use of trimethylsilyl iodide (TMSI), a well-known reagent for the removal of PMB ethers, only resulted in the hydroquinone mixture (Entry 4). The PMB group is also

known to be acid labile, thus protic conditions were investigated. Using aqueous HCl (Entry 5) resulted in a mixture of xanthone **2.27a** and hydroquinones **2.66** and **2.77**; however, it was not until trifluoroacetic acid (TFA) in CH_2Cl_2 was used did we begin to have success with this chemistry.[133] The reaction between and **2.76a** TFA in CH_2Cl_2 provided only the hydroquinones in quantitative yield (Entry 6); however, by excluding oxygen and light from the reaction, the xanthone **2.27a** was isolated in >95% yield (Entry 7). As long as either oxygen (Entry 8) or light (Entry 9) was excluded from the reaction, the xanthone was isolated in good yield. Using neat TFA resulted in decomposition of the starting material (Entry 10), while stirring **2.76a** in CH_2Cl_2 in the presence of light had no observable effect (Entry 11). It was operationally simpler to perform the reactions under oxygen free rather than light free conditions, thus oxygen was removed by sparging the reaction mixture with Ar for a few minutes before and after TFA was added. Altering the solvent (Entries 12-15) had drastic effects on the product mixture, but the xanthone was never isolated as cleanly or in as good a yield compared to CH_2Cl_2. It deserves to be mentioned that using CCl_4 resulted in a 1:1 ratio of the xanthone **2.27a** with starting material **2.76a** in >95% yield (Entry 13). This could imply a disproportionation between the two compounds, but it does seem unlikely because a mixture (7:3) of **2.27a** and the hydroquinones was obtained when PhCl was used as the solvent. Use of other solvents such as acetone, Et_2O, MeCN, and PhOMe (data not shown) resulted in the recovery of starting material. The formation of the hydroquinones **2.66** and **2.77** under non-reducing conditions is interesting. Currently, we do not have a satisfactory answer for this reaction, but a tentative mechanism has been proposed.

Table 2.6 Deprotection and cyclization of PMB-protected keto-quinone



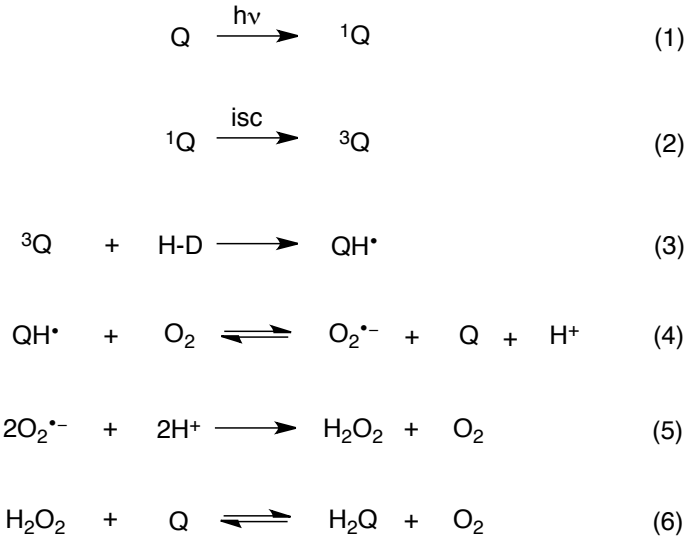
2.76a **2.27a** **2.77**: R = PMB; **2.66**: R = H

Entry	Conditions	Solvent	Ratio of **2.27a** : **2.77**+**2.66** (^{1}H NMR)	Yield (%)
1	DDQ, Δ	CH_2Cl_2, H_2O	--	--	RSM
2	CAN	MeCN, H_2O	--	--	RSM
3	Ph_3CBF_4	CH_2Cl_2	2	1	--
4	TMSI	$CHCl_3$	--	1	--
5	6 N HCl	dioxane	1	4	>95
6	TFA	CH_2Cl_2	--	1	>95
7	TFA, no O_2, no hν	CH_2Cl_2	1	--	>95
8	TFA, no O_2	CH_2Cl_2	1	--	>95
9	TFA, no hν	CH_2Cl_2	1	--	>95
10	TFA	neat	--	--	dec.
11	hν	CH_2Cl_2	--	--	RSM
12	TFA	MeOH	--	1:1 with RSM	>95
13	TFA	CCl_4	1:1 with RSM	--	>95
14	TFA	PhCl	7	3	>95
15	TFA	THF	--	--	dec

When **2.76** was stirred in a solution of TFA, CH_2Cl_2, under ambient oxygen and light, a mixture of the xanthone **2.27a** and the hydroquinones **2.66** and **2.77** was obtained in good yield. One potential mechanism that could account for these results can be proposed (Figure 2.1). It is well known that quinones are capable of photoexcitation from the ground state to the excited singlet state via a "forbidden" n-π* transition under ambient light (1).[134] From here the quinone is capable of intersystem crossing to the highly reactive triplet state (2). It is then plausible that hydrogen atom abstraction from a reagent (CH_2Cl_2, TFA, etc.) could occur (3).[135] Next, the hydroquinone radical could react with ambient O_2 to provide the peroxide radical anion, the starting quinone and a proton (4). In a disproportionation reaction, two quinone radicals could combine with

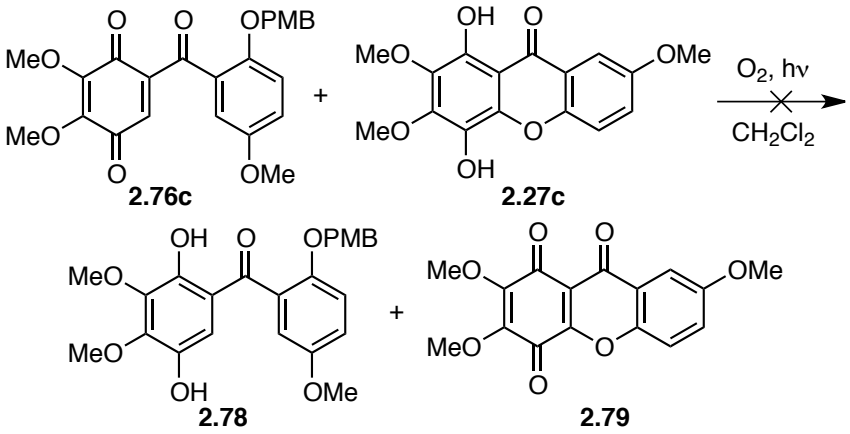
ambient O_2, generating hydrogen peroxide and singlet oxygen (5).[136] Finally, the quinone could be reduced to the hydroquinone by hydrogen peroxide with liberation of singlet oxygen. This reduction has been reported with benzoquinone and hydrogen peroxide in the presence of solid acids.[137] While this proposed mechanism does address the issue of oxygen and light necessary for reduction, in a key experiment exposure of a keto-quinone to H_2O_2 in a separate experiment did not result in the reduction of the quinone.

Figure 2.1 Proposed mechanism of quinone reduction



In Entry 13 of Table 2.6, a mixture (1:1) of xanthone **2.27a** to starting material **2.76a** was obtained when CCl_4 was used as solvent. This interesting result led us to believe that a disproportionation could be taking place between the starting material and product. To probe this finding, a mixture of and keto-quinone **2.76** xanthone **2.27c** were stirred together in the presence of O_2 and light in CH_2Cl_2 (Scheme 2.17). After a prolonged reaction time, both of the starting materials were recovered in quantitative yield. This result convinced us that disproportionation between the xanthone and keto-quinone was not a viable mechanistic pathway.

Scheme 2.17 Unsuccessful disproportionation experiment

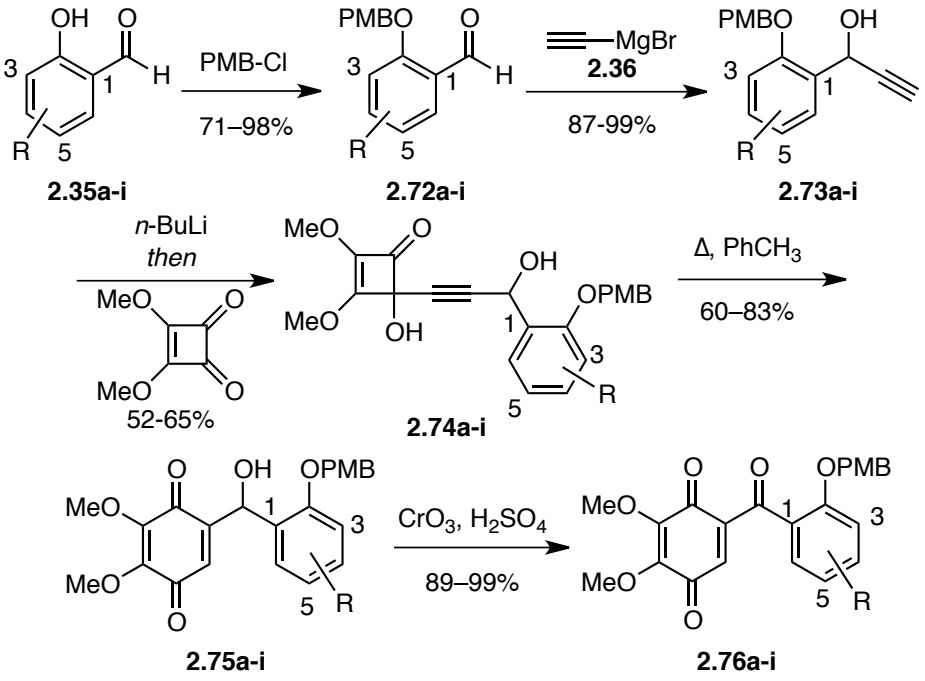


2.4 Exploration of the Substrate Scope

Now with a clear route to the deoxygenated xanthone core at our disposal, we were excited to explore the next phase of the project by expanding the substrate scope and targeting several xanthone natural products. Nine commercially available salicylaldehyde derivatives containing methyl, methoxy or chloride substituents at various locations on the aromatic ring were put through the sequence of reactions outlined in the preceding schemes. If the salicylaldehyde was prohibitively expensive, *o*-formylation of the respective phenol under known conditions readily provided the desired product.[138] Protection of the salicylaldehydes **2.35a-i** as their PMB ethers **2.72a-i** took place in 71-98% yield, and ethynylation provided **2.73a-i** in 87-99% yield (Scheme 2.18). For compounds **2.72a-i** and **2.73a-i**, recrystallization or filtration through a plug of silica gel afforded analytically pure compounds. The dianions of **2.73a-i** were formed with excess *n*-BuLi and then treated with a solution of **2.9** to afford diols **2.74a-i** in 52-65% yield. Because the diols tended to fragment to reform **2.9** and the aldehyde upon storage at -30 ˚C, they were typically heated in refluxing $PhCH_3$ to induce the Moore rearrangement to give quinones **2.75a-i** in 60-83% yield. Oxidation of the alcohols to the

ketones **2.76a-i** using chromic acid took place in 89-99% yield. The resulting keto-quinones were used without purification. See appendix for individual yields of the synthetic steps.

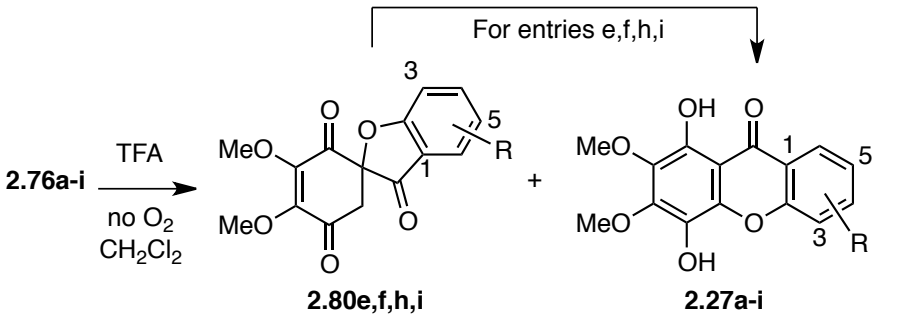
Scheme 2.18 Exploration of the substrate scope



The PMB group was removed from **2.76a-i** with TFA in deoxygenated CH_2Cl_2, and the resulting phenols underwent conjugate addition to deliver xanthones **2.27a-i**, spirocycles **2.80a-i** or inseparable mixtures thereof (Table 2.7). In Entries a-d,g, the xanthones were formed exclusively; no spirocycles were observed. In Entries e,f,i, mixtures of xanthones **2.27e,f,i** and spirocycles **2.80e,f,i** were obtained, while the spirocycle **2.80h** was isolated exclusively in Entry h. Rearrangements of spirocycles to

xanthones in similar systems are known to occur by heating the spirocycle in DMSO or $PhNO_2$, or sublimation at elevated temperatures under strong vacuum (*cf.* Scheme 1.14).[47,139] Thermally sensitive substrates would not withstand the forcing conditions. After some investigation, the rearrangements of the spirocycles **2.80e,f,i** to their respective xanthones were found to proceed readily upon exposure to K_2CO_3 in acetone. The rearrangement of spirocycle **2.80h** took place in EtOAc since the yield in acetone was lower (30% versus 63%). The overall yields of **2.27a-i** in this multistep sequence from alcohol **2.75a-i** ranged from 60-95%.

Table 2.7 Deprotection and cyclization of keto-quinones under oxygen free conditions



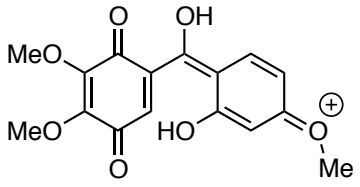
Entry	**2.80:2.27**[a]	**2.27a-i** (%)[b]
a: R = H	0:1	95
b: R = 3-OMe	0:1	77
c: R = 5-OMe	0:1	81[c]
d: R = 5-Cl	0:1	92
e: R = 4-OMe	1:2	83
f: R = 4-Me	1:4	76[d]
g: R = 4-Cl	0:1	63
h: R = 6-OMe	1:0	61
i: R = 6-Cl	7:2	60

[a] Isolated as an inseparable mixture; ratios determined by ^1H NMR spectroscopy; [b] overall yield from **2.75a-i**; [c] reaction required 24 h; [d] EtOAc was used as solvent for rearrangement; yield in acetone was 30%.

The different behavior of **2.76a-**i upon treatment with TFA was intriguing. We reasoned that substituent effects were at play, and suspected that steric factors, electronic

factors or combinations of both were involved. The xanthones **2.27a-d** with substitution at the C(3) and C(5) positions were isolated cleanly and no spirocycle was observed (Entries a-d); whereas electron rich groups at the C(4) position have a significant effect on the regiochemistry of the cyclization. The presence of a methoxy group (Entry e) resulted in a mixture (1:2) of **2.80e**:**2.27e**, while a methyl group (Entry f) gave a slightly higher ratio of spirocycle **2.80f** to xanthone **2.27f** (1:4). Electron release from a methoxy group into the carbonyl group, shown in resonance structure **2.81** (Figure 2.2), would be expected to lower the electron withdrawing capability of the carbonyl group. As a result, the quinone moiety would be less likely to undergo 1,4-addition and make cyclization to form the five-membered ring a competitive pathway. The weaker electron donating properties of a methyl substituent at C(4) affects cyclization to the spirocycle to a lesser extent, as is evident in a higher ratio of xanthone to spirocycle. We queried whether an electron withdrawing substituent at C(4) would show a reversal in selectivity by delivering the xanthone as the major product. When chloride substituted keto-quinone **2.76g** underwent deprotection, the xanthone **2.27g** was the only product formed; no spirocycle was detected in the reaction mixture. Based on the results of Entries e-g, we believe that the electronic nature of the C(4) substituent governs the regioselectivity of the cyclization.

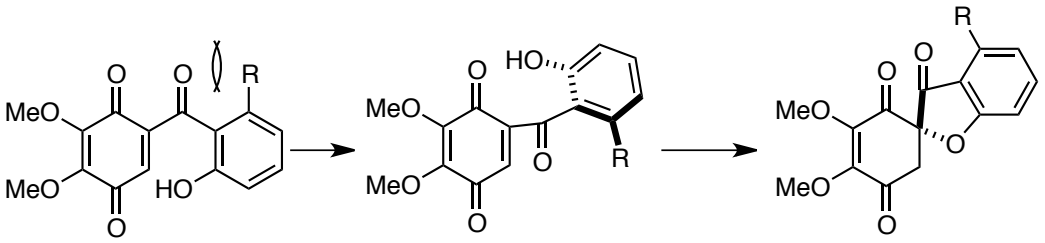
Figure 2.2 Proposed rationale for spirocycle formation with C(4) substitution



2.81

Substituents at the C(6) position of **2.81** display a combination of electronic and steric factors that influence the regiochemistry of the cyclization. A methoxy group at C(6) (Entry h) led to the formation of spirocycle **2.80h** as the only product. This could be due to the electron releasing properties that were observed with C(4) substitution. Steric factors could also be at play since the geometry necessary for cyclization to give **2.27** greatly increases the interaction between the methoxy group (R = OMe) and the carbonyl group shown in **2.82** (Figure 2.3). The steric requirements of the disubstituted ketone could force the phenol into a conformation such as **2.83**, which would then cyclize to form the spirocycle. A chloride atom at C(6) (Entry i) influences cyclization to some extent, as evidenced by formation of a mixture (7:2) of xanthone **2.27i** to spirocycle **2.80i**, but steric interactions do seem to be the dominant factor at C(6). The interplay between forming the spirocycle versus the xanthone has been observed before,[47,139] and the tentative proposal involving a combination of steric and electronic factors appears to address the issue of regioselectivity in the cyclization. This rationale also explains the spirocyclization for substrates discussed in Scheme 1.14 of Chapter 1. It can easily be envisioned that other electron withdrawing groups at C(6), such as a nitro or carbonyl containing functional group, would favor more of the xanthone. These compounds were not synthesized due to our other endeavors in applying the Moore rearrangement chemistry to the preparation of 1,4-dioxygenated xanthone natural products.

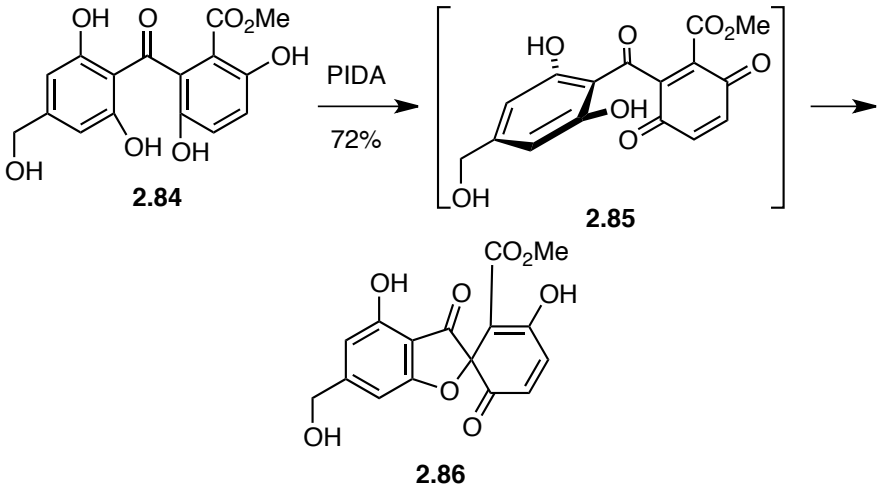
Figure 2.3 Proposed rationale for cyclization with C(6) substitution



2.82 **2.83** **2.80h**: R=OMe
2.80i: R=Cl

After we published the results for the spirocyclization, Porco and coworkers reported an interesting observation in their synthesis of graphisin A (Scheme 2.19).[140] Upon oxidation of **2.84** with periodobenzene diacetate (PIDA), the benzoquinone **2.85** was a proposed as an intermediate *en route* to the spirocycle **2.86**, which was obtained in 72% yield. The disubstituted carbonyl group of intermediate **2.85** is similar in structure to that of **2.82**. The rationale we proposed for cyclization to form the 5- or 6-membered rings can explain the results Porco sees in the cyclization; however, Porco proposed that spirocyclization is due to a low energy conformation of **2.85** brought on by favorable alignment of an *o*-phenol group with the π* orbital of a quinone carbon atom. While Porco's tentative hypothesis does explain the results for his particular substrate, no further studies were performed.

Scheme 2.19 Porco's proposal for spirocyclization



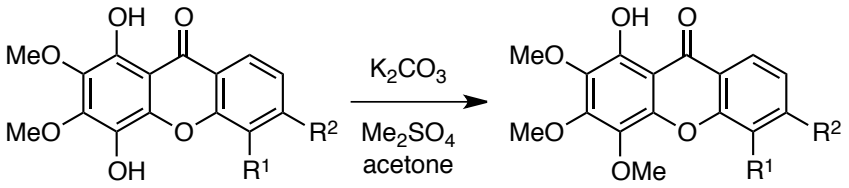
2.5 Synthesis of 1,4-Dioxygenated Xanthone Natural Products

2.5.1 Tetramethoxyxanthone Natural Products

Having established a new approach for the facile synthesis of 1,4-dioxygenated xanthones, we sought to apply it to the synthesis of selected xanthone natural products using intermediates that had already been prepared during the methodological studies. Thus, the tetramethoxy xanthones **2.87**[4] and **2.88**,[141] the biological activities of which were discussed in Chapter 1, were simply prepared by the regioselective methylation of **2.27b** and **2.27e** under basic conditions in 84% and 99% yields, respectively (Scheme 2.20).[24] Notably, the preparation of xanthone **2.87** in seven steps and in 22% overall yield represents a significant improvement over the previously reported synthesis.[16] The ^{1}H NMR spectral data of **2.87** were in agreement with those reported for the isolated natural product. Unfortunately, there were noteworthy differences in the ^{13}C NMR spectral data. A xanthone that has been labeled dulcisxanthone C was reported to have the structure of **2.88**; however, the ^{1}H and ^{13}C NMR spectral data reported for dulcisxanthone C do not match those for synthetic **2.88**, the structure of which was verified by single crystal x-ray

crystallography (see appendix).[141] Comparison of the ^{1}H and ^{13}C NMR spectral data of dulcisxanthone C actually correspond well to those obtained for synthetic **2.87**. Accordingly, we believe that the structure of dulcisxanthone C should be reassigned to that of **2.87**.

Scheme 2.20 Regioselective phenol methylation to afford natural products



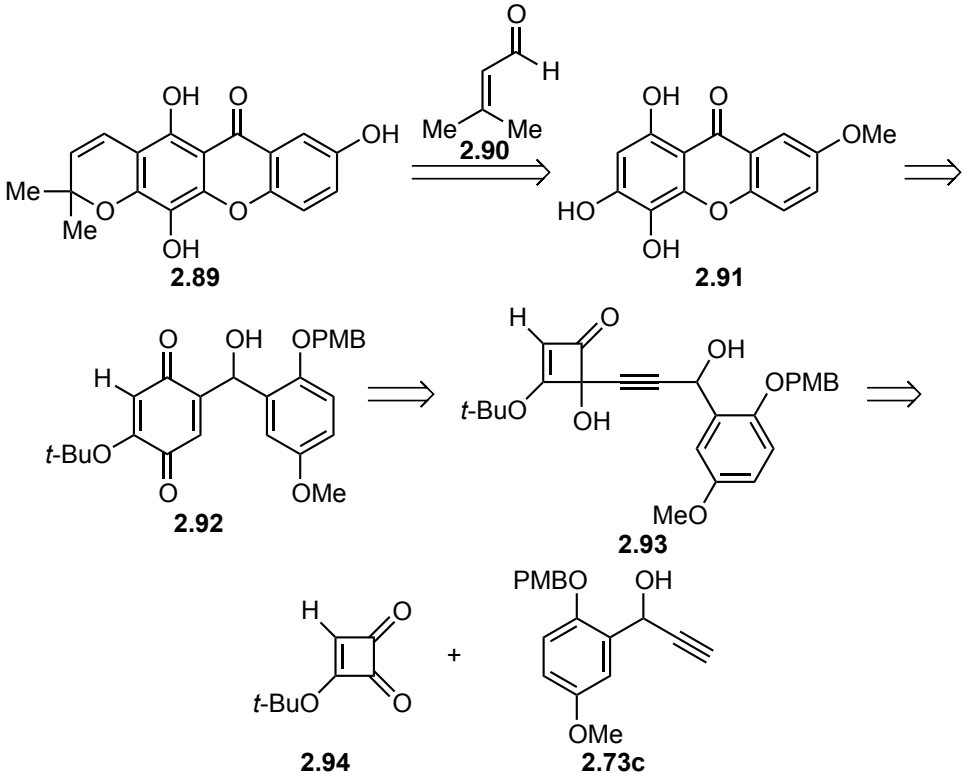
2.27b: R^1 = OMe, R^2 = H
2.27e: R^1 = H, R^2 = OMe

2.87: R^1 = OMe, R^2 = H (84%)
2.88: R^1 = H, R^2 = OMe (99%)

2.5.2 Attempted Synthesis of the Xanthone Atroviridin

Atroviridin (**2.89**) was previously synthesized by Theodorakis and Suzuki in thirteen and ten steps, respectively.[6,7] We thought the Moore rearrangement approach would allow a more facile route to this and other tetracyclic pyran-containing xanthone natural products (Scheme 2.21). In our plan, we envisioned that **2.89** would be obtained from xanthone **2.91** after incorporation of prenal (**2.90**) and deprotection of the aryl methoxy group. The triphenol **2.91** would arise from the oxidation and deprotection/cyclization of **2.92**, which would be obtained after the Moore rearrangement of **2.93**. Diol **2.93** is the product of the coupling between squarate **2.94** and alkyne **2.73c**.

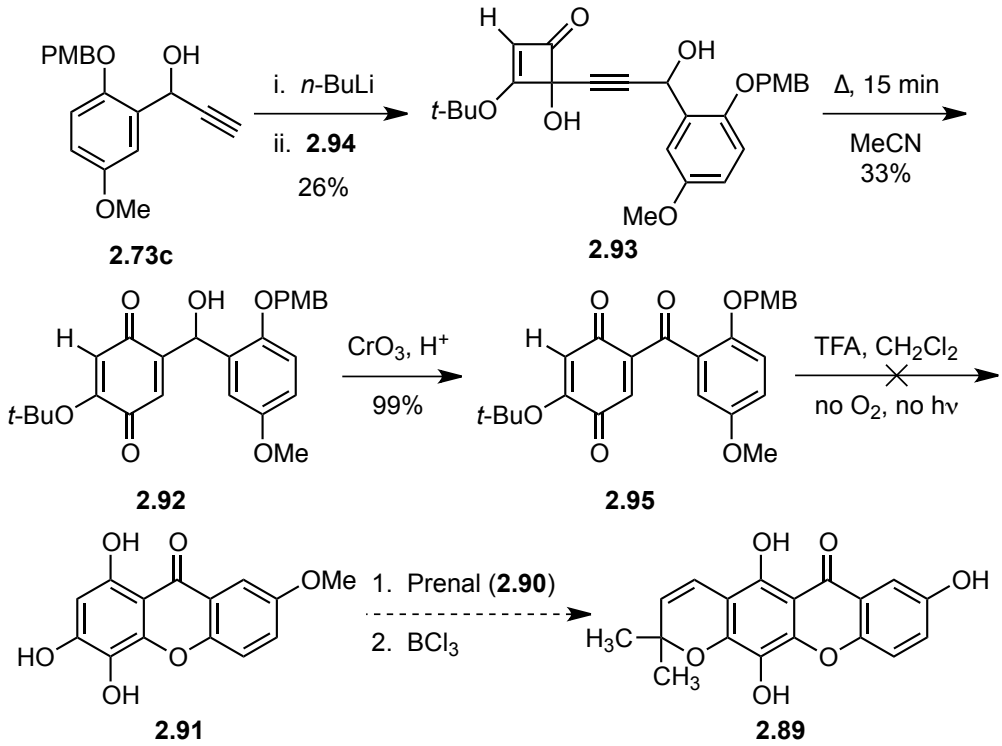
Scheme 2.21 First generation retrosynthesis of atroviridin



In accord with the chemistry outlined in Scheme 2.21, the dianion of **2.73c** was generated with *n*-BuLi and then treated with squarate **2.94** to deliver diol **2.93** in 26% yield (Scheme 2.22). The squarate **2.94** is readily available from squaric acid in two steps.[68] The Moore rearrangement of mono-substituted squarates such as **2.93** requires less forcing conditions than those with dimethoxy substitution.[68] In this case, the Moore rearrangement of **2.93** proceeded rapidly in 33% yield to the desired quinone **2.92** in refluxing MeCN. The alcohol moiety of **2.92** was oxidized to the ketone **2.95** using chromic acid in 99% yield. Unfortunately, the deprotection and subsequent cyclization of **2.95** to the xanthone **2.91** was not successful. Upon exposure of **2.95** to the TFA-mediated, oxygen-free deprotection conditions, several unidentified products were observed but the desired xanthone **2.91** was not observed. A mass consistent with that of

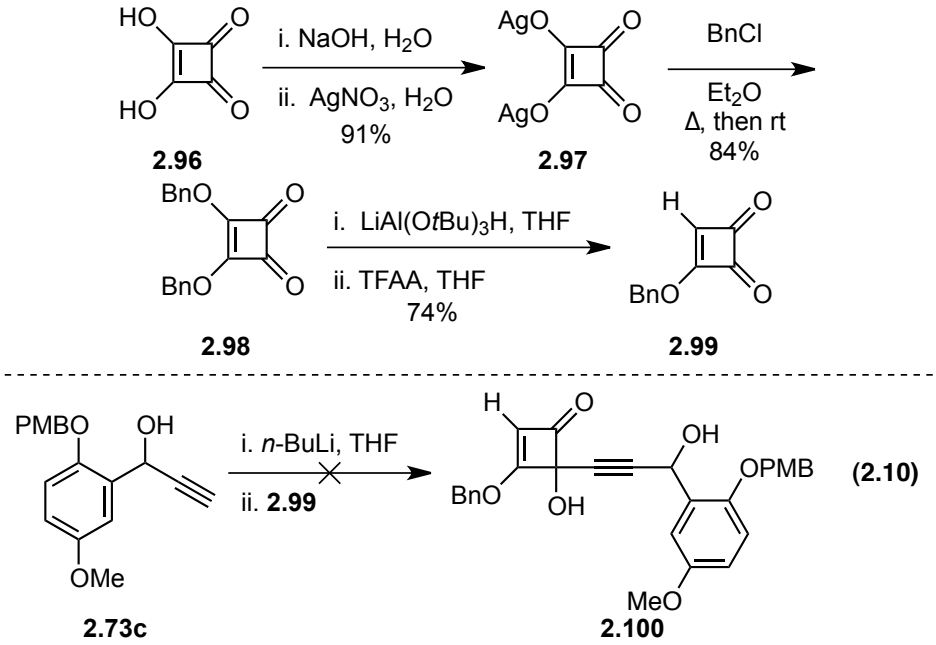
the desired xanthone **2.91** was not observed in the LC-MS data. In order to complete the synthesis of **2.89**, a regioselective cyclization with prenal (**2.90**) at the C(3) phenol would be followed by demethylation with BCl_3. One potential problem with the route concerned the deprotection and cyclization step. Based on the previous work with the project, we felt that the deprotection of the PMB group and subsequent cyclization would deliver a xanthone. There was also ample precedent for removal of *tert*-butyl groups from phenolic oxygen atoms using TFA solutions.[142] We were unsure if both steps could be accomplished in the same reaction sequence. After failing to obtain **2.91** by deprotection and cyclization, it became clear to us that a one-step sequence would not be an efficient means to obtain the tetraphenol **2.91**. We decided to prepare a squarate with a new protecting group that would survive the deprotection/cyclization sequence.

Scheme 2.22 Unsuccessful deprotection and cyclization on route to atroviridin



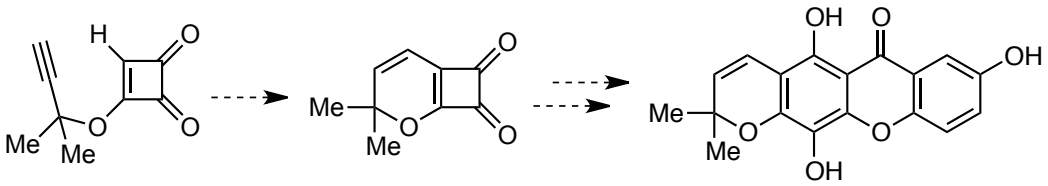
We queried whether a benzyl instead of a *tert*-butyl protecting group on the squarate moiety might allow access to a xanthone since the benzyl and PMB groups can be removed under orthogonal conditions (Scheme 2.23). The bis-sodium salt of squaric acid (**2.96**) was thus generated under basic conditions and treated with $AgNO_3$ to afford the squaric acid disilver salt **2.97** in 91% yield.[143] Exposure of **2.97** to benzyl chloride gave dibenzyloxy squarate **2.98** in 84% yield. Reaction of **2.98** with $LiAl(O\textit{t}Bu)_3H$ followed by dehydration with TFAA provided mono-benzyloxy squarate **2.99** in 74% yield.[144] Unfortunately, when **2.99** was treated with the dianion of **2.73c**, none of the desired squarate **2.100** was obtained even though starting material was consumed (Equation 2.10). One potential reason why the reaction may not have been successful is that the carbon atom alpha to the benzyloxy group is more susceptible to nucleophilic attack relative to a *tert*-butyl protecting group. Oftentimes, **2.73c** was the only isolable product in low yields from the reaction. In almost all attempts, the squarate **2.99** was never recovered from the crude reaction mixture. Since the benzyloxy-substituted squarate **2.99** failed to undergo the 1,2-addition, we queried whether a new strategy to the core of atroviridin involving a Claisen cyclization would be a more viable alternative.

Scheme 2.23 Synthesis of mono-benzyloxy squarate **2.99**



A new approach to atroviridin as well as other tetracyclic xanthones of similar structure was developed (Scheme 2.24). We were curious whether a Claisen cyclization of **2.101** to the dione **2.102** would be a more successful venture to the core of atroviridin (**2.89**) rather than the 1,2-addition of the dianion of **2.73c** with a squarate, which we have already established as low yielding (*cf.* Scheme 2.22). With the dimethyl pyran core already appended to the squarate portion, there would not be a need for a reaction with prenal at a late stage of the synthesis (*cf.* Scheme 2.21). The attempted preparation of **2.102** will be discussed in the following sections.

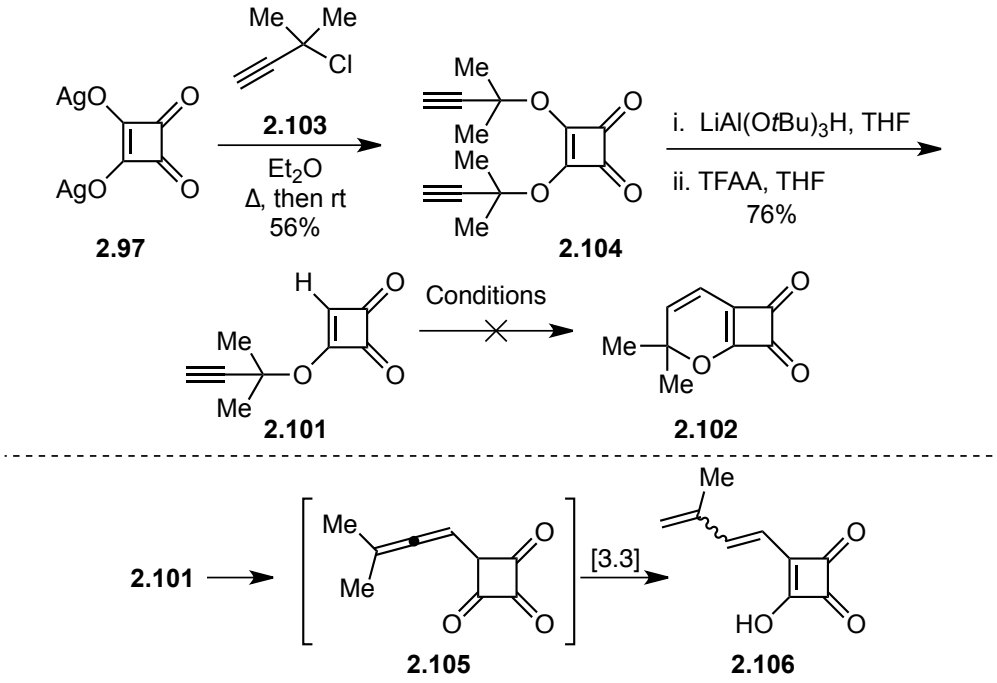
Scheme 2.24 Proposed use of dione **2.102** in a Claisen cyclization



2.101 **2.102** **2.89**

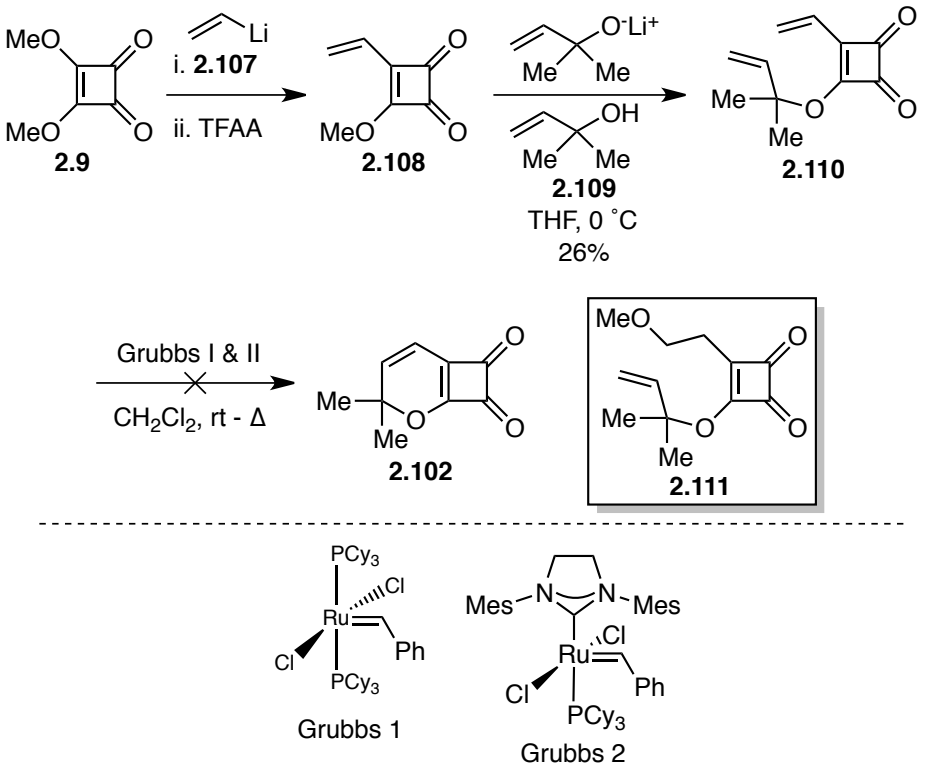
The disilver salt of squaric acid **2.97** was thus treated with propargyl chloride **2.103** to deliver the bis-alkylated squarate **2.104** in 56% yield (Scheme 2.25). The disubstituted squarate **2.104** was reduced with $LiAl(OtBu)_3H$ and subsequently dehydrated with TFAA to deliver the monosubstituted squarate **2.101** in 76% yield. We were now ready to begin searching for successful Claisen cyclization conditions. The first series of reaction conditions involved heating the squarate **2.101** in several solvents under reflux of in the microwave oven. In most cases, **2.101** was consumed but the desired product **2.102** was not detected in the crude reaction mixtures. The TLC of the reaction consisted of baseline material, and the residue after thermolysis was insoluble in most organic solvents. We reasoned that **2.101** may not be stable to elevated temperatures, thus we tried several cationic and acidic conditions to effect the cyclization. In all cases, the starting material was consumed but the reaction failed to produce any of the desired **2.102**. Based on available spectral evidence, the only isolable compound from a reaction was the conjugated diene **2.106**. The formation of **2.106** presumably comes from the intermediate ketene **2.105** after the Claisen rearrangement. We next pursued other routes to **2.102**.

Scheme 2.25 Attempted preparation of the cyclobutenedione **2.102**



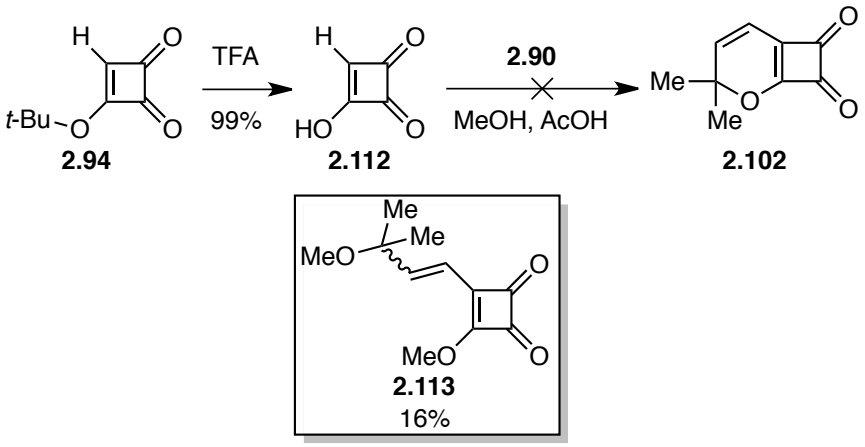
An alternative route to the cyclobutenedione **2.110** was next explored (Scheme 2.26). In the next route examine, dimethylsquarate (**2.9**) was treated with one equivalent of vinyllithium (**2.107**), and then dehydrated with TFAA to give **2.108** (Scheme 2.26). The squarate **2.108** was then treated with the lithium alkoxide of allyl alcohol **2.109** in THF at 0 ˚C to provide **2.110** in 26% yield. A significant portion of the mass balance was the side product **2.111**, where the displaced methoxide added in a 1,6-fashion to generate the ether product. All of the squarate **2.110** was exposed to Grubbs first and second-generation metathesis catalysts in CH_2Cl_2 with the goal of performing a ring closing metathesis to deliver the pyran **2.102**. Unfortunately, no reaction occurred at room temperature, and heating the reaction gave a complex mixture of products.

Scheme 2.26 RCM approach to the cyclobutenedione



One last attempt to obtain cyclobutenedione **2.102** was then examined (Scheme 2.27). Exposure of *tert*-butoxy squarate **2.94** to neat TFA delivered semisquaric acid (**2.112**) in quantitative yield.[145] Reaction of **2.112** with prenal (**2.90**) under mildly acidic conditions, however, gave none of the desired product **2.02**. Of the numerous byproducts formed during the reaction, **2.113** was isolated in 16% yield. This was an encouraging result because it provided evidence that **2.90** was undergoing reaction with **2.112**, but MeOH was reacting faster than cyclization could occur.

Scheme 2.27 Unsuccessful cyclization approach to the cyclobutenedione



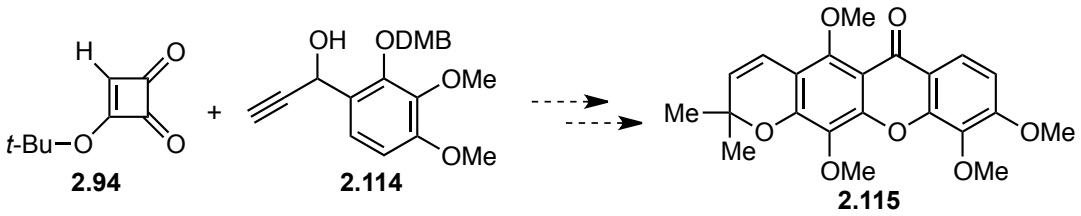
After these results, we were faced with an important decision. The attempted synthesis of atroviridin (**2.89**) was so far unsuccessful. The most advanced intermediate in the proposed synthesis we obtained was the keto-quinone **2.95** in the first generation route (*cf*. Scheme 2.22). The problem with that route was the deprotection and cyclization sequence, providing a complex mixture of unidentified products. When we switched targets to the dimethylpyran squarate **2.102**, we were unable to affect a Claisen cyclization. With these setbacks in mind, we put the atroviridin total synthesis project on hold so we could focus on other applications of the Moore rearrangement to 1,4-dioxygenated xanthone natural products.

2.5.3 Attempted Synthesis of Dulxanthone E

Concurrent with our efforts to synthesize atroviridin, other pyran-containing 1,4-dioxygenated xanthones were being investigated. One ongoing project at the time was the total synthesis of dulxanthone E (**2.115**). Dulxanthone E is a tetracyclic, linear, 1,4-dioxygenated xanthone with no reported prior syntheses.[146] The xanthone does not have reported biological activity, but other members[147] in its family exhibit useful biological properties such as anticancer[148] and antibacterial.[149] Since there was a problem with

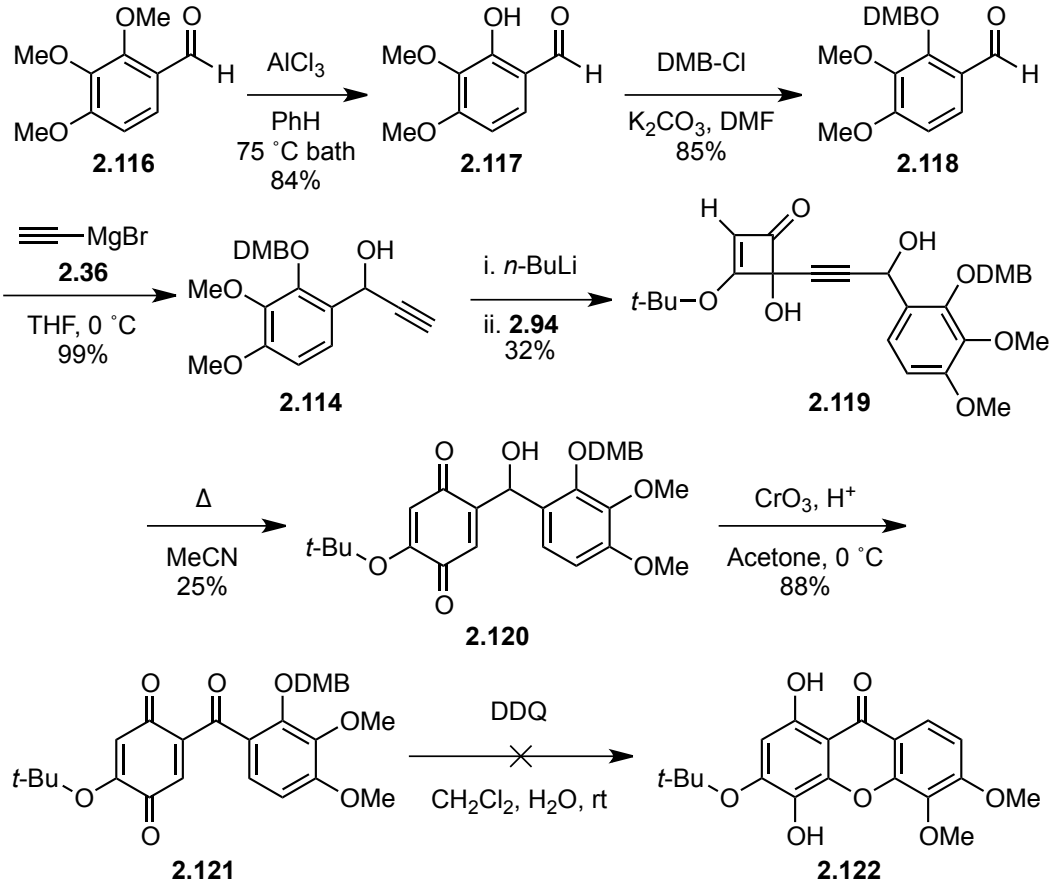
removal of the PMB group in a route toward atroviridin, we decided to switch to the 3,4-dimethoxybenzyl (DMB) protecting group. Because of its lower oxidation potential, the DMB group is even more readily cleaved by oxidants such as DDQ than the PMB group.[150] Dulxanthone E (**2.115**) would arise from the use of *tert*-butoxy squarate **2.94** and propargyl alcohol **2.114**, which is readily available from the corresponding trimethoxybenzaldehyde.

Scheme 2.28 Use of a DMB protecting group in the synthesis of dulxanthone E



The methoxy group *ortho* to the aldehyde moiety of **2.116** was demethylated regioselectively with $AlCl_3$ to deliver the salicylaldehyde **2.117** in 84% yield (Scheme 2.29). The DMB group was installed under basic conditions in 85% yield, and the resulting aldehyde **2.118** was ethynylated to provide alcohol **2.114** in 99% yield. The reaction of the dianion of **2.114** with squarate **2.94** proceeded in an unoptimized 32% yield to give the diol **2.119**. The Moore rearrangement of **2.119** proceeded under mild conditions to deliver the quinone **2.120** (25% yield), and the benzyl alcohol moiety of which was then oxidized to the ketone **2.121** with chromic acid in 88% yield. Unfortunately, all attempts to remove the DMB protecting group failed. Exposure of **2.121** to DDQ under a variety of conditions resulted in the recovery of starting material. Unfortunately, we no longer were able to prepare more of the keto-quinone **2.121** because the dianion reaction of **2.114** to diol **2.119**, and the Moore rearrangement of **2.119** were both difficult to reproduce. The yields for both sequences were also low.

Scheme 2.29 Unsuccessful preparation of dulxanthone E



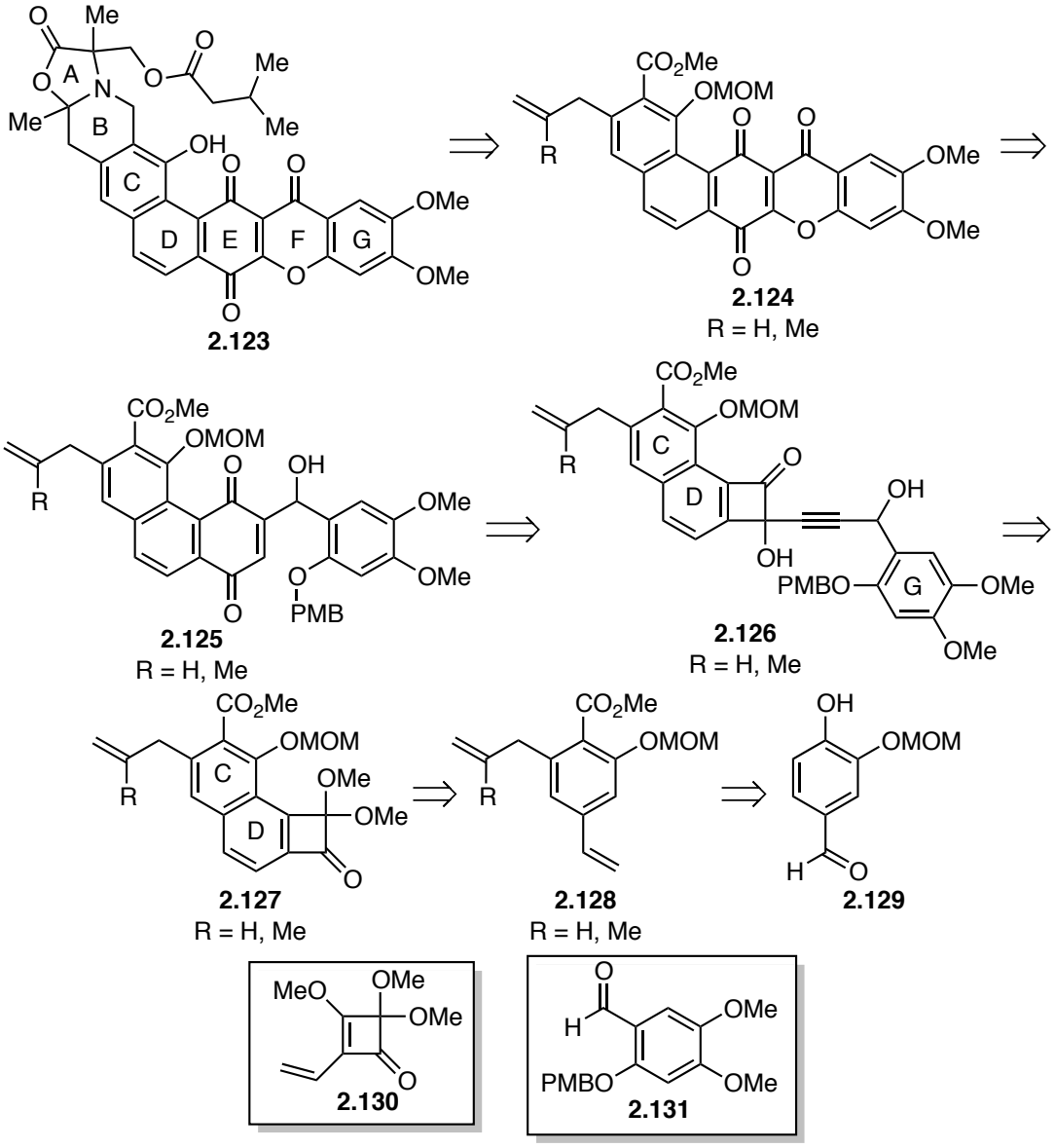
We were again facing a difficult decision with this aspect of the Moore rearrangement project. We could bring up more material to try alternative deprotection conditions for the DMB group, use a new protecting group altogether, or temporarily leave the realm of pyran-fused 1,4-dioxygenated xanthones for the pursuit of a new non-pyran containing natural product. The decision was actually simple considering the yields of the dianion reaction of **2.114** with **2.94** were poor, and the Moore rearrangement of **2.119** was difficult to reproduce. We decided to place the synthesis of pyran-containing 1,4-dioxygenated xanthone natural products such as atroviridin (**2.89**) and dulxanthone E (**2.115**) on hold while we next pursued the total synthesis of citreamicin α.

2.5.4 Efforts Toward the Synthesis of Citreamicin α (2.123)

The interest in the citreamicin α (**2.123**) project was in large part due to our ongoing efforts in the total synthesis of IB-00208 (**1.7**) and related xanthone compounds (*cf*. Figure 1.1). The structural similarities between citreamicin α (**2.123**) and IB-00208 (**1.7**) offer us a significant advantage in terms of synthetic planning since several proposed synthetic strategies in the retrosynthesis of **2.123** have already been applied to current efforts toward the synthesis of IB-00208. Furthermore, many challenging transformations and reaction conditions have also been optimized in the context of IB-00208. In principle, it should be possible to apply the reaction conditions optimized for IB-00208 to the synthesis of citreamicin α (**2.123**), thus enabling us to prepare the natural product rapidly and with minimal number of steps.

The retrosynthesis of citreamicin α (**2.123**) is shown in Scheme 2.30. We envision an ambitious late stage installation of the oxazolidinone A/B rings to the advanced C-G ring system of **2.124**. This will enable us to work with an achiral substrate until the last steps of the sequence, thus allowing us to prepare analogs of the natural product. The E ring of the C-G pentacyclic ring core **2.124** will be prepared from the quinone **2.125** after oxidation and subsequent deprotection/cyclization of the phenolic moiety. In a similar approach to that developed for IB-00208, the quinone ring will be formed from a benzocyclobutanone squarate **2.126** after the Moore rearrangement. The diol **2.126** will arise from the reaction of **2.127** with an alkyne and the PMB-protected salicylaldehyde derivative **2.131** using an acetylene stitching process. The CD naphthalene ring **2.127** will be derived from **2.128** after attachment of the squarate **2.130**.[144] Finally, the styrene derivative **2.128** will arise from the simple MOM-protected aldehyde **2.129**.

Scheme 2.30 The Martin group's approach to citreamicin α (**2.123**)

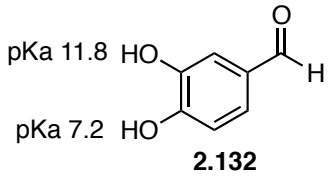


2.5.4.1 Preliminary studies in the total synthesis

The first task at hand was to prepare the aldehyde **2.129** in significant amounts. The material is available by a five-step sequence from 3,4-dihydroxybenzaldehyde (**2.132**).[151] A lengthy synthesis of the starting aldehyde is not the most efficient way to begin the natural product, so we envisioned accessing **2.129** *via* several potential routes.

We knew that selective protection of the *m*-phenolic oxygen atom of **2.132** was not feasible since the *m*-phenolic moiety is reported to be four pKa units higher than the *p*-phenolic hydroxyl group. The known dissociation constants of **2.132** are 7.2 for pKa_1 and 11.8 for pKa_2.[152] The difference in pKa values is presumably due to the *para* location of the C(4) hydroxyl group.

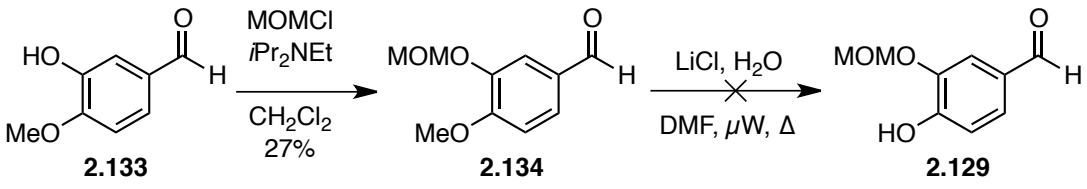
Figure 2.4 pKa values of 3,4-dihydroxybenzaldehyde



2.132

Since a direct one-step approach was not a viable option, a two-step procedure was investigated. Commercially available isovanillin (**2.133**) was treated with MOM-Cl under basic conditions to provide the aldehyde **2.134** in 27% yield (Scheme 2.31). Unfortunately, heating a mixture of **2.134** with LiCl in DMF in the microwave oven provided none of the desired aldehyde **2.129**. Instead, isovanillin (**2.133**) was recovered in 45% yield. None of the desired product was detected in the crude reaction mixture.

Scheme 2.31 Attempted synthesis of **2.129** from isovanillin

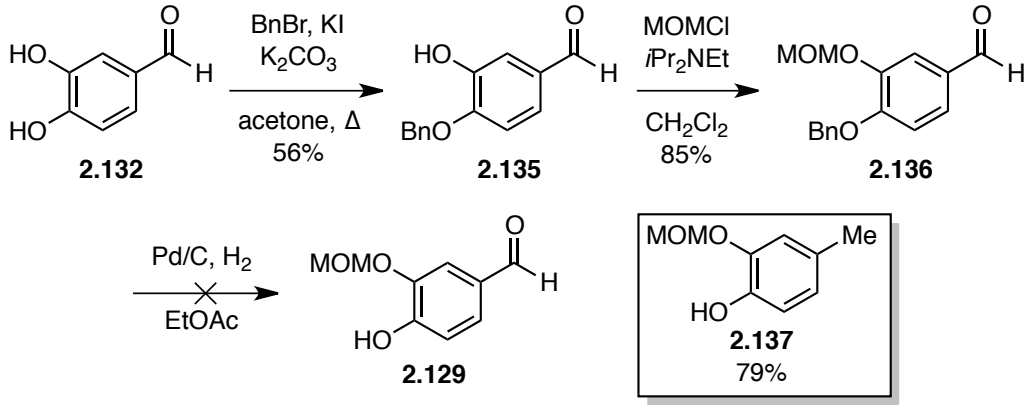


2.133 **2.134** **2.129**

We next decided to take advantage of the higher acidity of the *p*-substituted phenol by regioselectively benzylating **2.132** to deliver **2.135** in 56% yield (Scheme 2.32). No traces of the other potential side products were detected. The remaining phenol was protected with a MOM group to give the protected aldehyde **2.136** in 85%

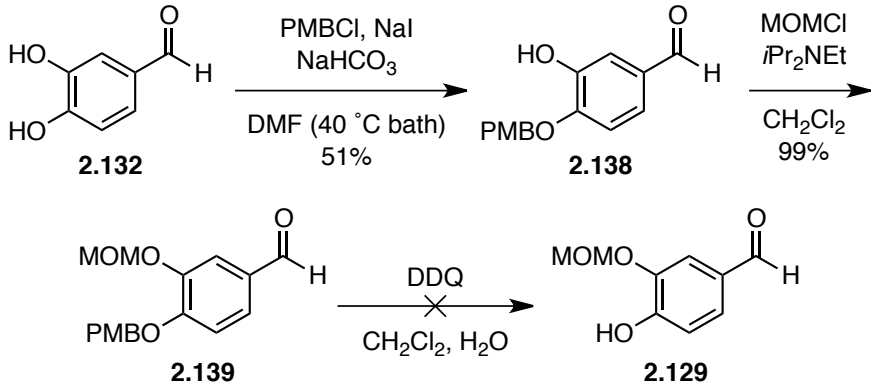
yield. Attempted hydrogenolysis of **2.136** under numerous conditions did not lead to the desired product **2.129**, giving instead the *p*-cresol derivative **2.137** in 79% yield.

Scheme 2.32 Unsuccessful hydrogenation approach to **2.129**



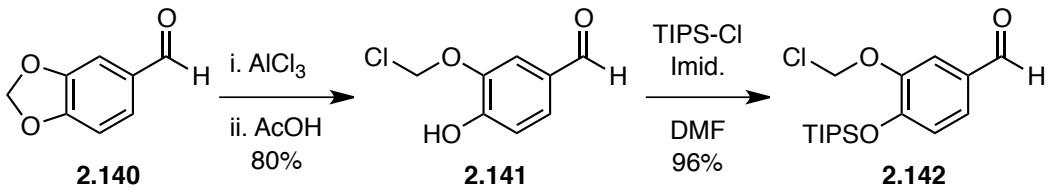
The next attempt to prepare **2.129** used a PMB group rather than a benzyl ether (Scheme 2.33). Regioselective protection of **2.132** as its PMB ether **2.138** proceeded in 51% yield. Protection of the remaining phenol as its MOM ether **2.139** occurred in quantitative yield. Frustratingly, upon exposure of **2.139** to DDQ in the presence of H_2O, a complex mixture of products was isolated. The desired **2.129** was not observed in the mixture.

Scheme 2.33 Unsuccessful PMB group removal to aldehyde **2.129**



Due in large part to the high number of setbacks to obtain **2.129** with our prior attempts, a different approach was developed. Amorim and coworkers reported that reaction of piperonal (**2.140**) with excess $AlCl_3$ followed by the addition of one equivalent of AcOH, gave the alkyl chloride **2.141** in 80% yield.[153] In our own hands, the yield of **2.141** was reproducible, and **2.141** was surprisingly stable to column chromatography and recrystallization (Scheme 2.34). All that was needed in order to convert **2.141** to **2.129** was to incorporate one equivalent of MeOH with a net displacement of HCl. Before these studies began, the phenolic moiety of **2.141** was protected as its triisopropylsilyl (TIPS) ether **2.142** in 96% yield because of a concern about the potential reaction between the phenoxide of **2.141** and the chloride to reform **2.140** under basic conditions.

Scheme 2.34 Ring opening of piperonal with $AlCl_3$

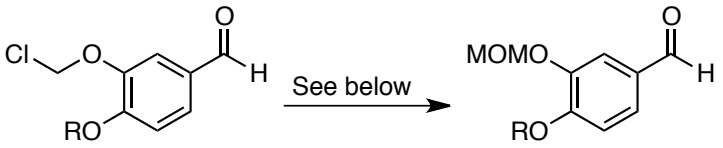


The conversion of **2.142** to the MOM derivative is simple in principle, but it turned out to be quite difficult in practice (Table 2.8). The first set of conditions consisted of stirring **2.142** with MeOH and iPr$_2$NEt, but a complex mixture of products was obtained (Entry 1). Next, **2.142** was heated with a stoichiometric amount of methoxide that was generated by treating MeOH with NaH in DMF (Entry 2). Surprisingly, piperonal (**2.140**) was recovered in quantitative yield, presumably forming from the attack of methoxide on the TIPS group and subsequent cyclization.

We then queried whether the desired product would form simply from stirring **2.142** in MeOH (Entry 3). Surprisingly, **2.132** was isolated in 75% yield. The working

hypothesis for this result was that the desired product was actually being formed under the reaction conditions, but it was losing the MOM group. The HCl that was displaced by MeOH could be responsible for the deprotection. After analyzing the products formed in the previous reactions, a different strategy was developed. The idea of using MeOH as a solvent was attractive since that was the source of the nucleophile, but the formation of large quantities of methoxide led to the formation of piperonal (**2.140**). Performing the reaction in the presence of strong bases led to the formation of **2.140**, while **2.132** was obtained if no base was present. Both of these results inspired us to search for bases that would form small amounts of methoxide during the reaction, and would also neutralize the HCl that was generated. A variety of weak bases were thus screened. Using $MgSO_4$ or sodium citrate (Entries 4 and 5) as bases provided an inseparable mixture of the desired **2.143** and **2.132** in 66 and 67% yields, respectively. When $NaHCO_3$ or Na_2HPO_4 were used as bases, the desired **2.143** was obtained in 58% and 86% yields, respectively. There was no evidence that any of the side products **2.140** and **2.132** were formed during the reaction. We then queried whether the methanolysis could be performed on the unprotected phenolic moiety of **2.141**. We were delighted to see that the desired MOM-protected compound **2.129** was isolated in 72% yield with no formation of byproducts (Entry 8).

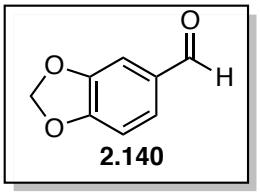
Table 2.8 Studies toward methanolysis of the alkyl chloride **2.156**



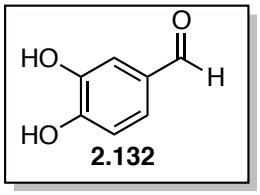
2.142: R = TIPS
2.141: R = H

2.143: R = TIPS
2.129: R = H

Entry	R	Conditions	Solvent	Result	Yield (%)
1	TIPS	MeOH, iPr$_2$NEt	CH_2Cl_2	dec	--
2	TIPS	NaH, MeOH	DMF	**2.140**	99
3	TIPS	--	MeOH	**2.132**	75
4	TIPS	$MgSO_4$	MeOH	4:1 **2.143**:**2.132**	66
5	TIPS	sodium citrate	MeOH	7:2 **2.143**:**2.132**	67
6	TIPS	$NaHCO_3$	MeOH	**2.143**	58
7	TIPS	Na_2HPO_4	MeOH	**2.143**	86
8	**H**	Na_2HPO_4	MeOH	**2.129**	72



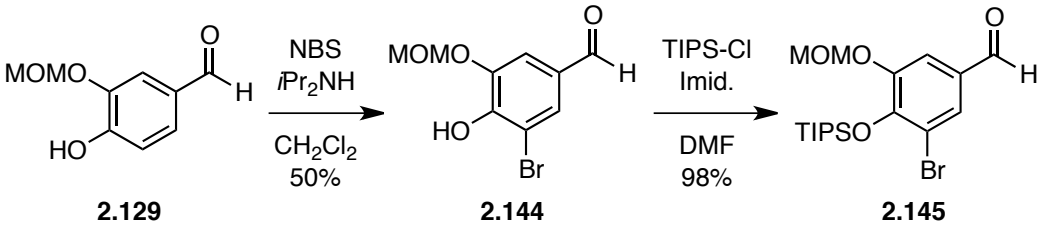
2.140



2.132

The next step in the proposed synthesis was the regioselective bromination of **2.129** *meta* to the aldehyde moiety. Bromination of **2.129** with NBS delivered **2.144** in ~30% yield alongside products suffering bromination at regioisomeric positions. When the same reaction was performed in the presence of iPr$_2$NH, the desired **2.144** was obtained in 50% yield (Scheme 2.35). The presence of secondary amine additives has been shown to increase the yield of bromination reactions *ortho* to phenolic moieties.[154,155] Small amounts of brominated regioisomeric products were present, but a recrystallization afforded a single product. The TIPS group was then installed on **2.144** to provide **2.145** in 98% yield.

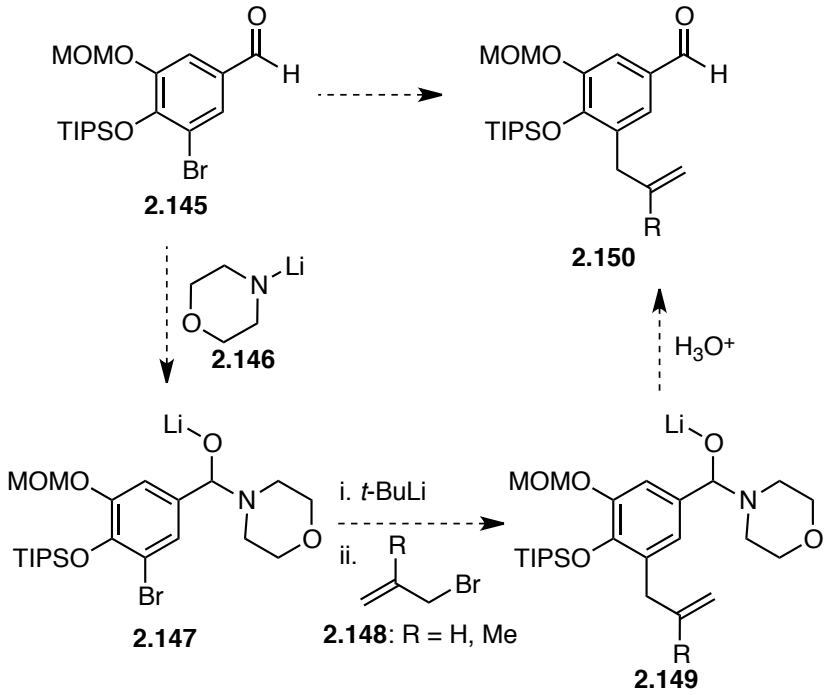
Scheme 2.35 Successful bromination of **2.129**



2.129 **2.144** **2.145**

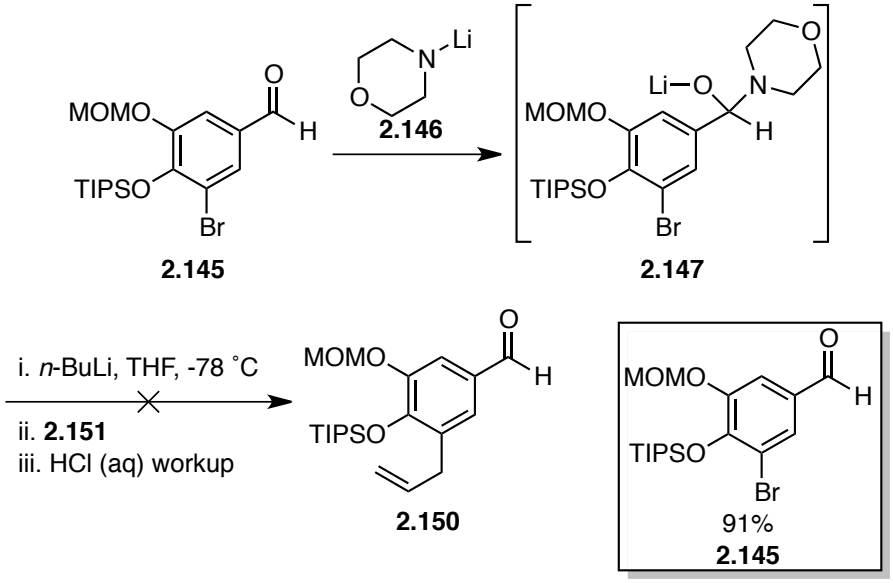
In order to attach the allyl fragment, a unique aldehyde protection strategy was adopted (Scheme 2.36). We envisioned that reaction of **2.145** with the anion of morpholine **2.146** would generate the addition product **2.147**.[156] Lithium-halogen exchange of **2.147** with excess *t*-BuLi would generate an aryllithium species that would then react with the alkylating agent **2.148** to deliver **2.149**. The tetrahedral intermediate **2.149** would collapse to reform the aldehyde **2.150** upon acidic workup. Other *in situ* protecting group strategies such as *N,N,N'*-trimethylethylenediamine,[157] *N,O*-dimethylhydroxylamine HCl,[158] and $Ti(NEt)_4$[159] have also been used.

Scheme 2.36 Application of an *in situ* aldehyde protecting group strategy



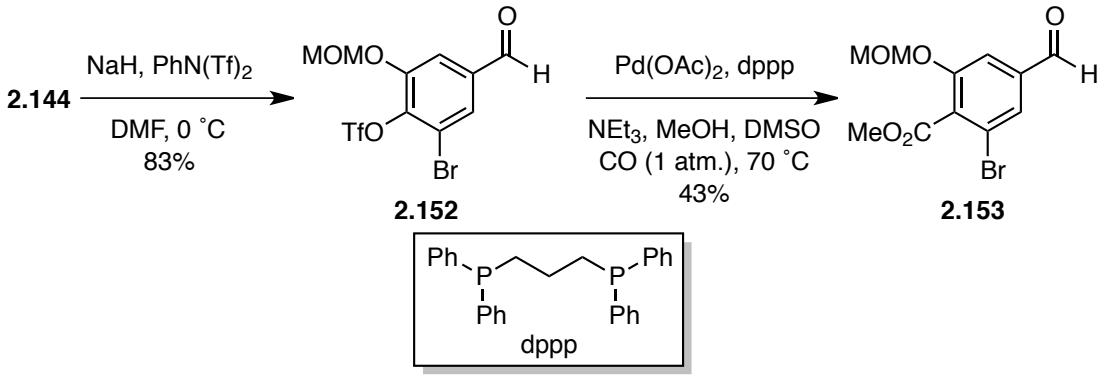
In a model study, allyl bromide (**2.151**) was used as the electrophile because it is known to undergo nucleophilic attack from lithiated aryl species.[160] In the event, reaction of **2.145** with the morpholine anion **2.146** presumably formed adduct **2.147** (Scheme 2.37). The aryl anion was presumably generated with excess *t*-BuLi, and allyl bromide (**2.151**) was then added. After an acidic workup, none of the desired allylation product **2.150** was detected in the crude reaction mixture. Instead, the starting material **2.145** was recovered in 91% yield implying that a proton source in the reaction had quenched the anion or that the anion was not formed. The starting aldehyde was dried by azeotropic removal of H_2O with PhH before use, but presumably there was still an adventitious source of water in one of the reagents. This minor setback did not dissuade us from pursuing this reaction further; however, concurrent with our investigations with the reaction in Scheme 2.37, another facet of the synthesis was under study.

Scheme 2.37 Unsuccessful application of the aldehyde protection strategy



We were next interested in forming the methyl ester portion of **2.128** by functionalization of the phenolic oxygen atom. The phenolic hydroxy group of **2.144** could be activated as the aryl triflate and then undergo a palladium-catalyzed, carbonylative cross-coupling. In the event, triflation of **2.144** using $PhN(Tf)_2$ with NaH as base gave **2.152** in 83% yield (Scheme 2.38). Other triflating reagents and bases led to poor yields and complex product mixtures. Carbonylation of **2.152** to the methyl ester **2.153** took place in 43% yield when diphenylphosphinopropane (dppp) was used as the ligand and DMSO as solvent. Use of other phosphine ligands resulted in poor yields of the carbonylated product **2.153**. The carbonylation proceeded with excellent regioselectivity because only the triflate underwent reaction; no bromide suffered carbonylation under the reaction conditions. This type of selectivity has been reported elsewhere in the literature.[161-163] We now felt that it was time to investigate the reaction by which to incorporate the squarate **2.130**.

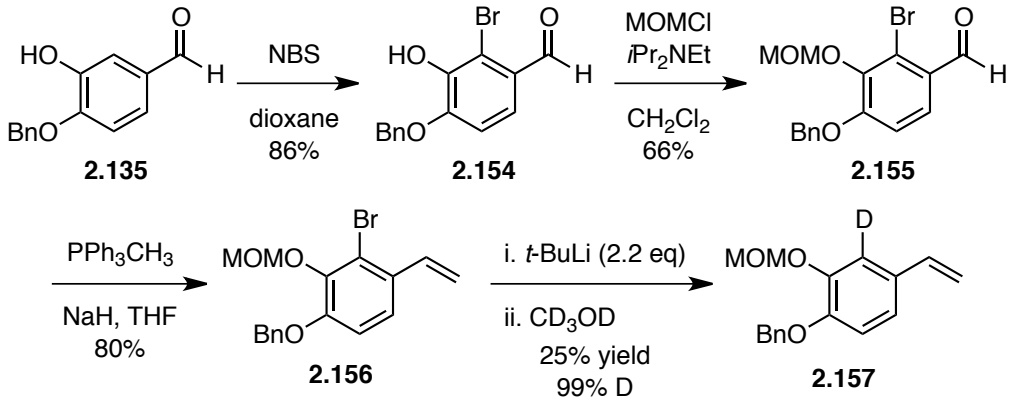
Scheme 2.38 Carbonylative cross-coupling of the aryl triflate **2.52**



The incorporation of the squarate **2.130** with an aryl aldehyde was inspired by the work on the total synthesis of IB-00208 (**1.7**).[77] Bromination of **2.135** with NBS delivered the tetra-substituted aromatic **2.154** with good regioselectivity *ortho* to the phenol group in 86% yield (Scheme 2.39). The undesired brominated regioisomers could be separated by recrystallization. The regioselectivity of the bromination is in line with reports by Cha and coworkers.[164,165] Protecting of the phenolic oxygen atom in **2.154** gave the protected compound **2.155** in 66% yield. The aldehyde moiety of **2.155** was subsequently olefinated under typical Wittig conditions to give **2.156** in 80% yield.

Bearing in mind the previously unsuccessful lithium-halogen exchange (refer to Scheme 2.39), we first decided to quantify the amount of aryl anion of **2.156** that was formed. After an extensive search of conditions, time, and temperature, the best result obtained for **2.157** was 99% deuterium incorporation, but a 25% yield of product. A significant portion of the mass balance was polymerized material, which is frequently seen when styrene derivatives are exposed to strong organometallic bases. Switching the order of addition did not increase the mass recovery.

Scheme 2.39 Model deuterium incorporation reactions on **2.135**

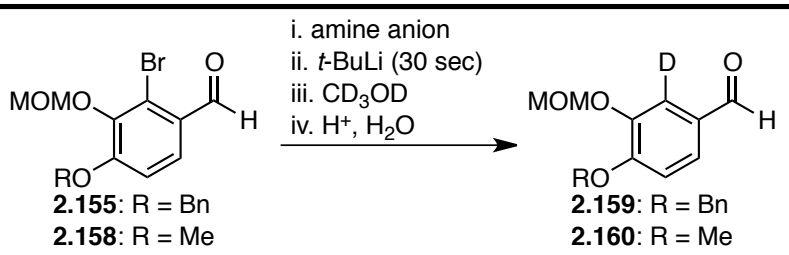


Since polymerization of the styrene moiety was a problem, we reinvestigated the *in situ* protection of the aldehyde. We also discovered an interesting report that showed the use of *N,O*-dimethylhydroxylamine HCl is superior to morpholine for the aldehyde protection.[158] We decided to screen both amines under lithium-halogen exchange conditions and determine the amount of deuterium incorporation (Table 2.9). The aldehyde **2.155** was treated with the morpholine anion **2.146**, which was then followed by lithium-halogen exchange with *t*-BuLi. Unfortunately, quenching the reaction with CD_3OD afforded none of the deuterated product **2.159** (Entry 1). The starting aldehyde **2.155** was recovered in 17% yield, the proteo-debrominated **2.161** was isolated in 36% yield, and products derived from starting material were isolated in 22% for a 75% mass recovery. The identical reaction was performed using NHMeOMeHCl as the amine (Entry 2), which requires two equivalents of *n*-BuLi to generate the respective amine anion. After quenching the reaction with CD_3OD, **2.155** was recovered in 22% yield, **2.161** was obtained in 56% yield, and products derived from starting material were recovered in 18% yield for a combined mass recovery of 98%. No products containing deuterium were isolated from the reaction. Although there was no deuterium incorporation with the previous two experiments, we did learn that NHMeOMeHCl not

only gave a higher mass recovery, but also resulted in a much cleaner reaction mixture. Accordingly, we no longer used morpholine for the *in situ* aldehyde protection.

The results of Entries 1 and 2 indicate that the lithium/halogen exchange was occurring to considerable degree, but a proton source quenched the anion faster than it could react with deuterium. We were confident that the proton source was not from **2.155** because it was first dried by azeotropic removal of H_2O with PhH and then placed under vacuum for 30 min. This suggested that the only possible remaining proton source was the amine. We decided to test this by forming the amine anion in the presence of the indicator Ph_3CH (Entry 3). The benzyl-protected aldehyde **2.155** was no longer available so we switched to the methylated analog **2.158**. Prior to this experiment, we believed the first equivalent of *n*-BuLi would react with the HCl and the second would react with the amine; any adventitious H_2O would lead to incomplete anion formation. In the presence of an indicator, the complete formation of the anion would be quantified by a strong color change when the excess *n*-BuLi reacted with Ph_3CH. When the aldehyde **2.158** was mixed with a slight excess of the quantitatively formed amine anion, treated with *t*-BuLi, and quenched with CD_3OD, we were absolutely thrilled to see that the desired **2.160** was isolated in 99% yield and 99% deuterium incorporation. This provided strong supporting evidence that the proton source came from the amine, not the aldehyde. With this result in hand, we turned our attention to the coupling of the aldehyde **2.158** and the squarate **2.130**.

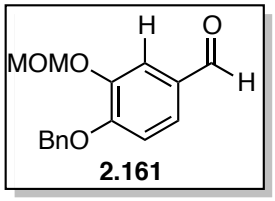
Table 2.9 Deuterium incorporation studies with the aryl bromide



2.155: R = Bn
2.158: R = Me

2.159: R = Bn
2.160: R = Me

Entry	R	Amine	Result
1	Bn	Morpholine	**2.155** (17%), **2.161** (36%), other (22%)
2	Bn	NHMeOMeHCl	**2.155** (24%), **2.161** (56%), other (18%)
3	Me	NHMeOMeHCl + Ph_3CH	**2.160** (99%), 99% D incorporation

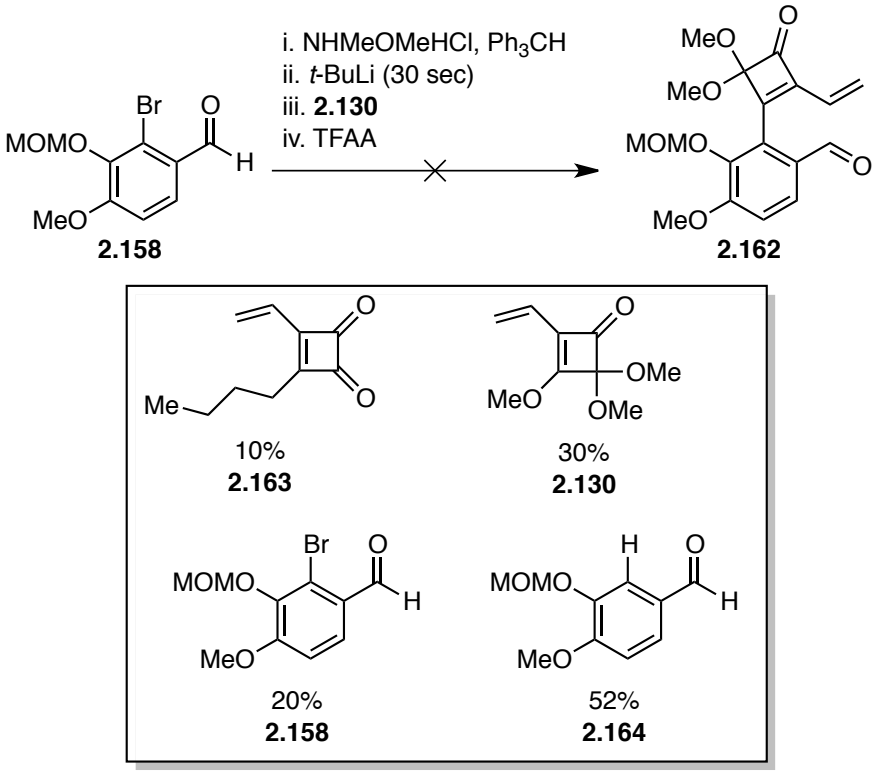


2.161

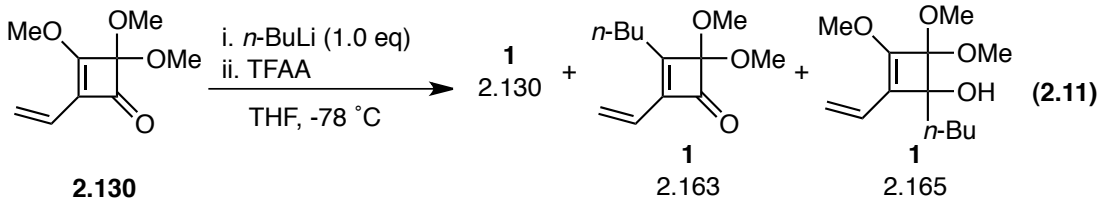
The anion of NHMeOMeHCl was generated in the presence of Ph_3CH and reacted with **2.158** (Scheme 2.40). The putative alkoxide adduct was treated with *t*-BuLi, the squarate **2.130** was added, TFAA was then added, but after a workup, none of the desired product **2.162** was isolated. Instead, the squarates **2.163** and **2.130** were isolated in 10% and 30% yields, respectively. The butylated squarate **2.163** is formed from the reaction of **2.130** with excess *n*-BuLi followed by dehydration with TFAA. The proteo-debrominated aldehyde **2.164** was recovered in 52% yield, and the starting aldehyde **2.158** was isolated in 20% yield. This result is strikingly different than what was obtained in Table 2.9, Entry 3. Since the aryl anion of **2.158** was quenched before it could react with the squarate, we believe there is a proton source associated with the squarate. The reactions in Scheme 2.40 and Entry 3 of Table 2.9 were performed simultaneously with the only difference being addition of the squarate to one and CD_3OD

to the other. Our next direction was to determine the amount of this unknown proton source that is associated with the squarate.

Scheme 2.40 Attempted coupling of the aldehyde **2.158** and squarate **2.130**



The squarate **2.130** was dried by azeotropic removal of H_2O, placed under vacuum for 30 min, and then treated with exactly one equivalent of *n*-BuLi followed by dehydration with TFAA (Equation 2.11). Surprisingly, a mixture (1:1:1) of three products was obtained: the starting squarate **2.130**, the butylated squarate **2.163** and the 1,2-addition product **2.165**. The latter two arise from the desired reaction of *n*-BuLi with the squarate. The data suggest a protic impurity is present in the squarate in the amount of approximately 30%.



This is currently where the route to citreamicin α (**2.123**) stands at this time. The next series of experiments will be aimed at removing or neutralizing the unknown protic impurity that is associated with the squarate **2.130**. The squarate will first be distilled from a drying agent. This would be the most effective way to remove the impurity. Stirring **2.130** with a base such as KH or NaH would be a second set of conditions to remove the impurity. If that fails, the squarate can be titrated with a strong base in the presence of an indicator, applying the same tactic that was used in Entry 3 of Table 2.8.

2.6 Summary and Conclusion

In summary, the Moore rearrangement was successfully applied to the synthesis of 1,4-dioxygenated xanthones and xanthone natural products. We first obtained a xanthone using a silicon-tethered protecting group such as **2.44** (Table 2.3); however, the yields were not reproducible and we were forced to protect the phenol in a revised route (Scheme 2.13). After screening several protecting groups, we discovered that the PMB protecting group provided the highest yield of the xanthone after deprotection (Table 2.6). We also discovered that removal of the PMB group from the phenolic oxygen atom of keto-quinones **2.76a-i** required exclusion of light, oxygen, or both in order to prevent the formation of hydroquinones **2.66** and **2.77** (Table 2.6). Upon cyclization of the phenolic oxygen atom with a quinone carbon atom, we observed the formation of spirocycles, xanthones, or mixtures thereof (Table 2.7). The preference seemed to arise from a combination of steric and electronic factors on the aromatic ring. A tentative

hypothesis was proposed satisfactorily explains the formation of the spirocycle (Figures 2.2 and 2.3).

The next course of action was the successful preparation of 1,4-dioxygenated xanthone natural products **2.87** and **2.88** using the Moore rearrangement. The characterization data of **2.88** were not consistent with the spectral data that were reported in the isolation paper; thus we were able to reassign the structure of dulcisxanthone C to that of the known natural product **2.87**. The previously reported synthesis of **2.87** required ten steps and 2.1% overall yield,[16] whereas the preparation of the same natural product using the Moore rearrangement as the key step delivered the natural product in seven steps and 22% overall yield. This is a marked improvement over the previous route in terms of overall yield, step count, and efficiency.

Using the Moore rearrangement has given us access to advanced intermediates in the synthesis of atroviridin (**2.89**) and dulxanthone E (**2.114**) as seen in Schemes 2.22 and 2.29. The total synthesis of citreamicin α (**2.123**), a highly complex angularly fused quinone xanthone natural product, was then undertaken using chemistry that was discovered within the Martin group. In the context of citreamicin α, we discovered a unique two-step reaction sequence to the preparation of a MOM-protected benzaldehyde derivative **2.129** that is reported[151] to take five steps in low yield (Table 2.7). Currently, other applications of the Moore rearrangement to the synthesis of 1,4-dioxygenated xanthones are ongoing.

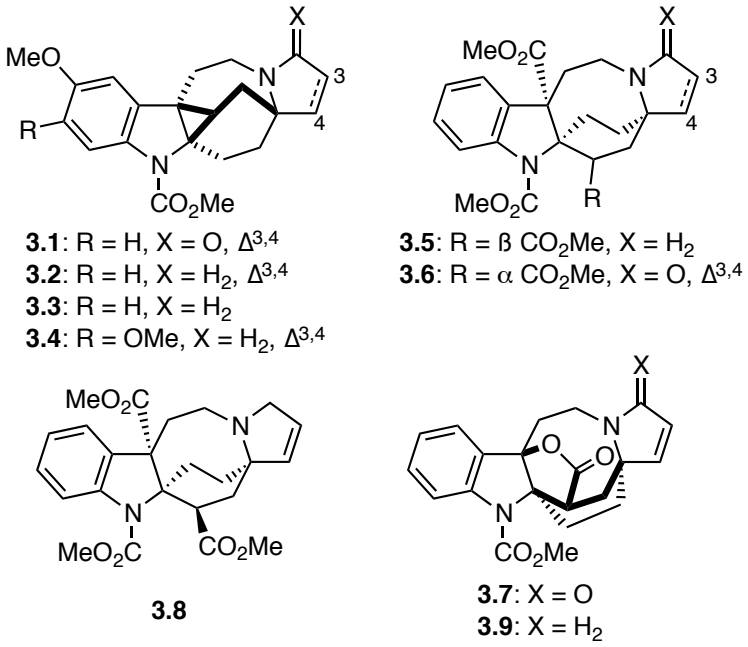
Chapter 3: The Synthesis of the Lundurine Natural Products

3.1 Selected Alkaloids from the *Kopsia* Genus

Extracts of the *Kopsia* plant are rich in alkaloid natural products, many of which exhibit useful biological properties and complex molecular architectures (Figure 3.1).[166] Lundurines A-C (**3.1**-**3.3**) were isolated in 1995, whereas lundurine D (**3.4**) was first reported in 2004.[167,168] In addition to lundurines A-D, grandilodines A-C (**3.5**-**3.7**) as well as lapidilectines A (**3.8**) and B (**3.9**) were also isolated from plants of the *Kopsia* genus.[166,169]

The lundurines have several notable structural features in common: each hexacyclic lundurine contains a dihydroindole core fused to a three- and eight-membered ring, with two of the three carbon atoms of the cyclopropane ring being fully substituted. Lundurines B (**3.2**) and D (**3.4**) were reported to exhibit *in vitro* activity against B16 melanoma cells with IC_{50}'s of 2.8 μg/mL and 7.2 μg/mL respectively.[168] Lundurine B (**3.2**), lapidilectine B (**3.9**), and grandilodines A (**3.5**) and C (**3.7**) were also reported to be effective in circumventing multidrug-resistance in vincristine resistant KB cells with IC_{50}'s of 4.6 μg/mL, 0.39 μg/mL, 4.35 μg/mL and 4.11 μg/mL respectively, making these compounds potential anticancer agents.[169] It is interesting to note that lundurines A and C do not have reported biological activity, perhaps owing to saturation and oxygenation of the five-membered heterocycle. In addition to having synthetically challenging structures, the biological activity of the lundurines make this class of compounds an ideal target for total synthesis. Of the alkaloids shown in Figure 3.1, only lapidilectine B (**3.9**) has succumbed to total synthesis.[170,171] Other work in the *Kopsia* family has been reported by several synthetic groups.[172-174] Most of the work in this area of total synthesis has been directed toward the lundurines; however, there have been no total syntheses to date.

Figure 3.1 Selected alkaloids of the *Kopsia* genus



3.1: R = H, X = O, $\Delta^{3,4}$
3.2: R = H, X = H_2, $\Delta^{3,4}$
3.3: R = H, X = H_2
3.4: R = OMe, X = H_2, $\Delta^{3,4}$

3.5: R = ß CO_2Me, X = H_2
3.6: R = α CO_2Me, X = O, $\Delta^{3,4}$

3.8

3.7: X = O
3.9: X = H_2

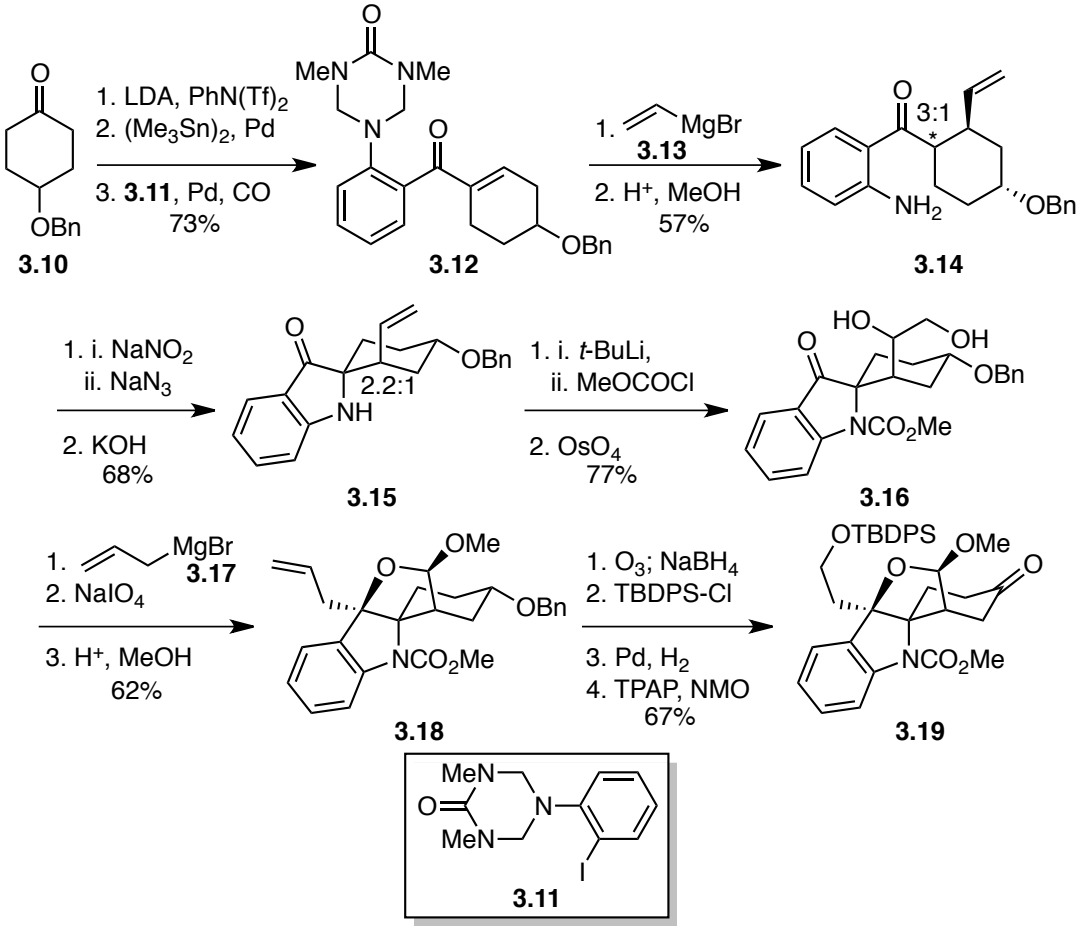
3.2 SELECTED STUDIES OF THE *KOPSIA* ALKALOIDS

3.2.1 Pearson's Synthesis of lapidilectine B

Pearson and coworkers reported the only synthesis to date of a *Kopsia lapidilecta* alkaloid (Scheme 3.1).[170,171] The first stages of the synthesis involved conversion of cyclohexanone **3.10**[175] to a vinyl triflate[176] that was subjected to a Stille cross-coupling with hexamethylditin.[177] A carbonylative Stille coupling between the prepared vinyltin species and aryl iodide **3.11**[178] delivered enone **3.12** in 73% overall yield. Enone **3.12** suffered conjugate addition with vinyl magnesium bromide (**3.13**) under Lipshutz conditions,[179,180] and the aniline was unmasked under acidic conditions to furnish the acetophenone **3.14** in 57% overall yield as a mixture (3:1) at the epimeric carbon. The aniline was diazotized with $NaNO_2$ under acidic conditions, and the resulting diazonium salt was treated with NaN_3 to give an aryl azide via nucleophilic aromatic substitution. The enolate of the ketone underwent a cyclization[181,182] with the aryl azide to provide the

indolin-3-one **3.15** in 68% overall yield as a mixture (2.2:1) of diastereomers at the C(2) position of indole. The indole *N*-H was protected as its methyl carbamate, and the vinyl group underwent dihydroxylation upon reaction with OsO_4 to deliver **3.16** in 77% overall yield. The carbonyl group of **3.16** was stereoselectively allylated with excess allylmagnesium bromide **3.17**, and the 1,2-diol was cleaved with $NaIO_4$. The aldehyde thus generated suffered attack by the benzylic alcohol to generate an intermediate lactol, that was subsequently exposed to acidic MeOH to deliver the methyl acetal **3.18** as a single diastereomer in 62% overall yield. The allyl group of **3.18** underwent ozonolysis and then reductive workup with $NaBH_4$ to give an alcohol that was subsequently protected as its TBDPS ether. The benzyl group was then removed under transfer hydrogenation conditions, and the alcohol was oxidized to the ketone with TPAP[113] to give **3.19** in 67% overall yield. With **3.19** in hand, Pearson and coworkers began studying their key transformation.

Scheme 3.1 Pearson's approach to lapidilectine B

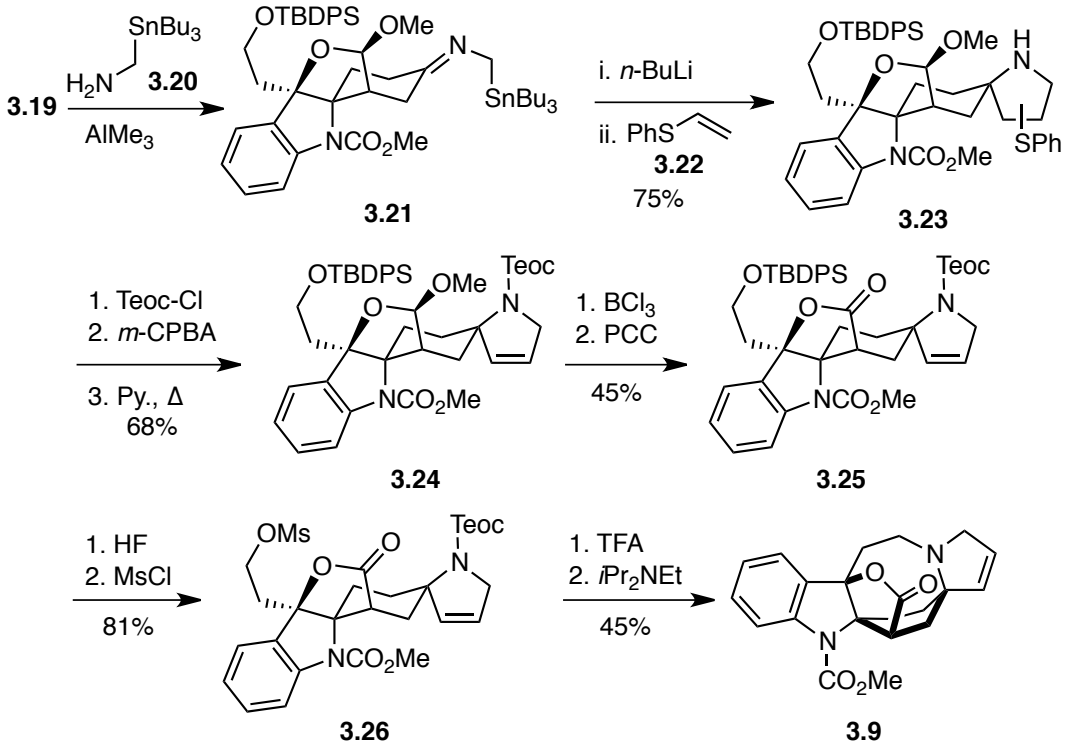


One of the key steps in Pearson's synthesis of **3.9** was the installation of the pyrroline ring using an elegant allyl amine cyclization strategy that had been developed in their laboratories. The ketone **3.19** was first condensed with (aminomethyl)tributylstannane[183] (**3.20**) in the presence of $AlMe_3$ to provide **3.21** (Scheme 3.2). Exposure of **3.21** to *n*-BuLi induced a lithium/tin exchange, and the resulting allyl amine underwent cyclization with phenylvinyl sulfide (**3.22**) to deliver **3.23** as a complex mixture of regioisomers, stereoisomers, and amide rotamers in 75% overall yield. The pyrrolidine moiety was protected as its 2-trimethylsilylethyl carbamate (Teoc), and the sulfide was oxidized to a sulfoxide, which upon heating was eliminated to

furnish the 3-pyrroline **3.24** in 68% yield over the three steps. Methyl acetal **3.24** was unmasked with BCl_3 which was then oxidized with PCC to the lactone **3.25** in 45% yield. The TBDPS group was removed, and the alcohol was mesylated to deliver **3.26** in 81% overall yield. Finally, the Teoc group was removed with TFA, and the resulting trifluoroacetate salt underwent an S_n2 displacement in the presence of $i Pr_2NEt$ to provide the natural product **3.9** in 45% yield.

This synthesis features several key transformations including the formation of the eight-membered ring, the sequence by which the pyrroline ring was installed, and the enolate cyclization onto the aryl azide to provide spirocycle **3.15**. The synthesis of **3.9** was achieved in 24 steps in 1.2% overall yield. Although the first and only synthesis of a member of the *Kopsia lapidilecta* family does deserve mention, the overall synthesis suffers from a high step count, multiple low yielding sequences, and poor facial selectivity in the enolate cyclization and the vinyl conjugate addition.

Scheme 3.2 Completion of lapidilectine B (**3.9**)

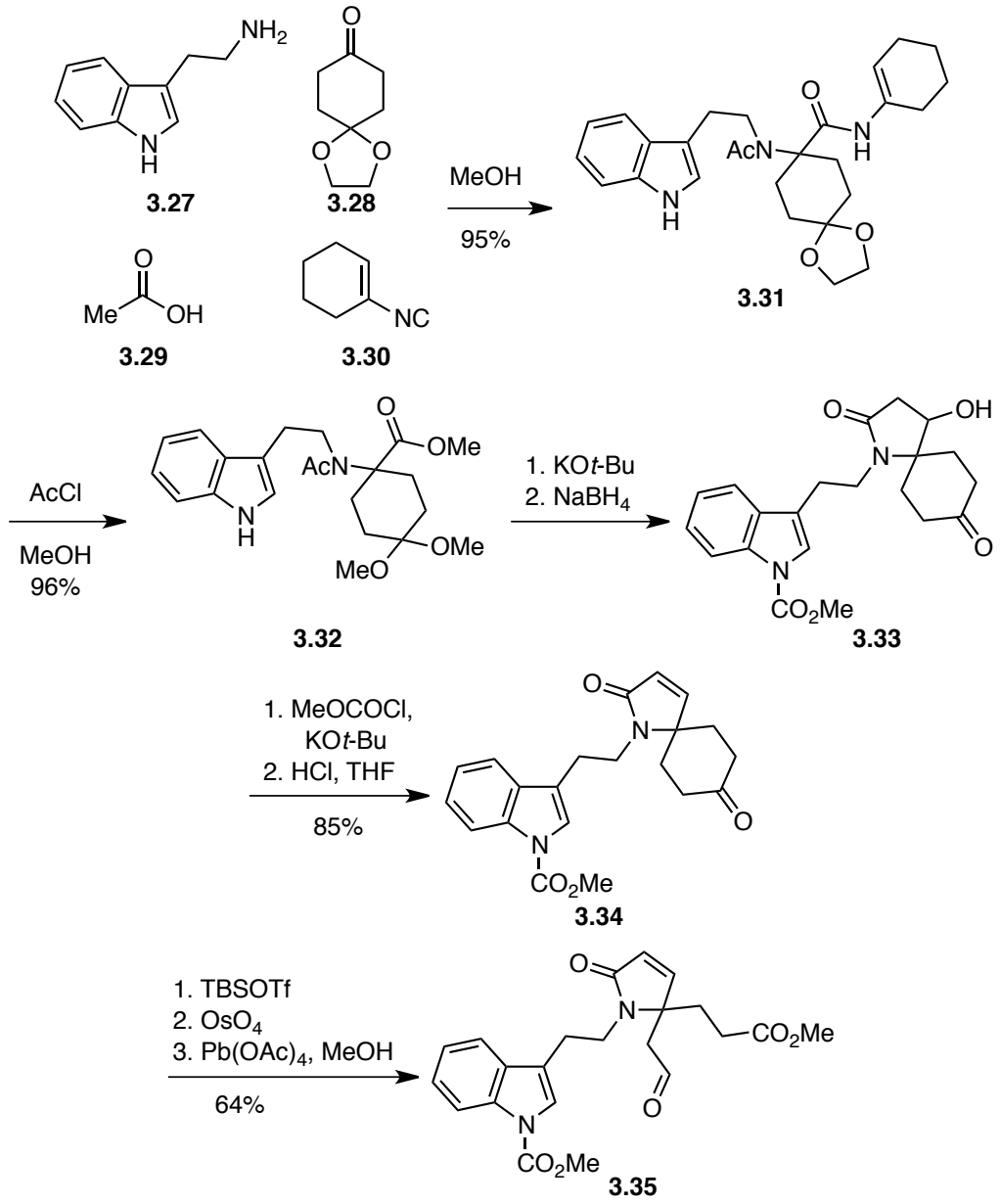


3.2.2 Efforts reported by Sarpong

Sarpong and coworkers reported a unified approach to the *lapidilectine* alkaloids in which numerous alkaloids (Figure 3.1) might be obtained from a single starting material.[184] The synthesis began with an Ugi multicomponent reaction[185,186] of tryptamine (**3.27**), ketal **3.28**, acetic acid (**3.29**), and isocyanide **3.30**[187] in MeOH to provide the pentacyclic product **3.31** in 95% yield. Notably, the multicomponent reaction could be performed on >200 gram scale without a decrease in yield. Following precedent first reported by Sorensen,[188] exposure of **3.31** to anhydrous HCl in MeOH afforded the methyl ester with concomitant transketalization to the dimethylketal **3.32** in 96% yield. Again borrowing precedent from Sorenson and coworkers,[188] exposure of **3.32** to basic conditions induced a Dieckmann condensation with the methyl ester, and subsequent

reaction with $NaBH_4$ selectively reduced the ketone to the alcohol **3.33**. Treatment of the resulting alcohol with methyl chloroformate acylated both the indole *N*-H and the alcohol, which spontaneously eliminated under the reaction conditions, thus establishing the unsaturation of the spirocyclic lactam of **3.34**. The ketone was then unmasked to provide **3.34** in 85% yield over a four-step sequence. The silyl enol ether of **3.34** was formed under standard conditions, and the enol ether underwent oxidative cleavage to the aldehyde **3.35** in 64% overall yield. With intermediate **3.35** in hand, the cyclization to form the eight membered ring was subsequently explored.

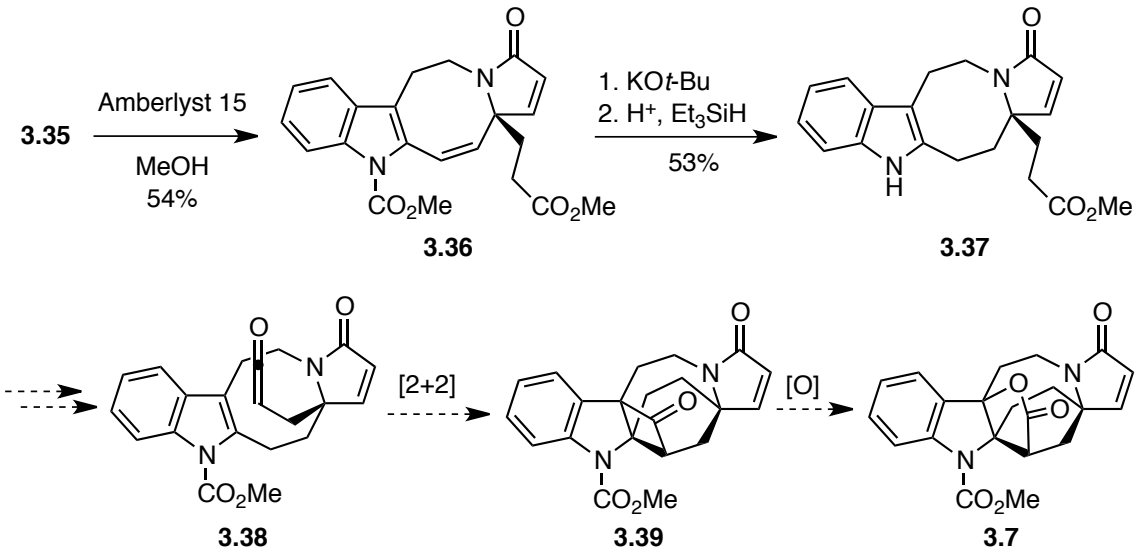
Scheme 3.3 Sarpong's approach to the *Kopsia* alkaloid core



After an extensive search of reaction conditions, Sarpong and coworkers discovered that exposure of aldehyde **3.35** to MeOH in the presence of an acidic resin delivered a dimethyl acetal. The dimethyl acetal subsequently underwent a Friedel-Crafts type reaction, suffering attack from the 2-position of indole, to provide the tetracycle **3.36**

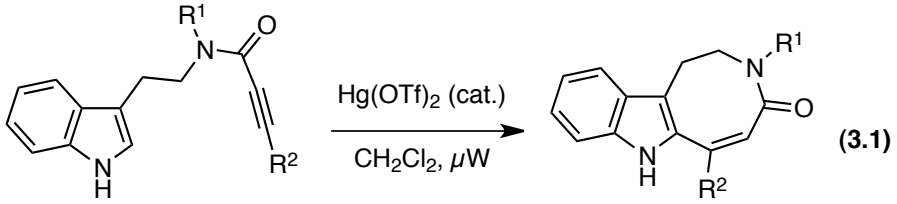
in 54% yield (Scheme 3.4). The indole was deprotected, and the olefin of the eight-membered ring was subsequently reduced under ionic conditions to give the saturated system **3.37** in 53% overall yield. Ongoing efforts within their group are now aimed at the elaboration of **3.37** to the natural products shown in Figure 3.1. The authors envisioned activation of the ester to a reactive ketene such as **3.38**, which would then undergo a [2+2] cycloaddition with the 2,3-positions of indole to give the cylobutanone **3.39**. A Baeyer-Villager oxidation of the ketone would deliver the lactone natural product grandilodine C (**3.7**). A decarbonylation of cyclobutanone **3.39** followed by cyclopropanation would deliver access to the lundurines if the aryl ring was appropriately substituted with a methoxy group on the 5-position. This route features an elegant application of the Ugi reaction, which provides rapid access to an advanced core. Additionally, the tetracycle **3.35** was obtained in decent yield using a unique cyclization approach under relatively mild reaction conditions.

Scheme 3.4 Sarpong's route to the tetracyclic core of the *Kopsia* alkaloids



3.2.3 Other Methods to the Lundurine Core

Van der Eycken and coworkers published a method by which eight-membered nitrogen containing azocine rings could be appended to the 2,3-positions of indole under mild conditions to give products such as **3.41** from ynamides **3.40** (Equation 3.1).[189] In the event, the alkyne moiety of the ynone **3.40** was activated by $Hg(OTf)_2$ to induce the electronically controlled regioselective cyclization onto the C(2) position of the indole. $Hg(OTf)_2$ was the only reagent that induced cyclization in catalytic quantities, and microwave heating led to higher yields and shorter reaction times compared to conventional heating. Although the approach was successful with a broad range of substrates (R^1 and R^2 = Ar and alkyl), there were notable shortcomings. First, protection of the indole *N*-H as its acetate or tosylate afforded none of the desired cyclization products. The inductive effects of an electron withdrawing protecting group on the indole *N*-H presumably disfavor cyclization onto the ynamide. Second, only tertiary amides cleanly underwent cyclization, whereas secondary amide (**3.40**, R^1 = H) resulted in intractable mixtures. This could arise from the s-*cis* versus s-*trans* geometry on the secondary amide of **3.40**.[190] Finally, cyclizations of terminal alkynes (**3.40**, R^2 = H) required prolonged reaction times (48 h) and were low yielding (<26%).

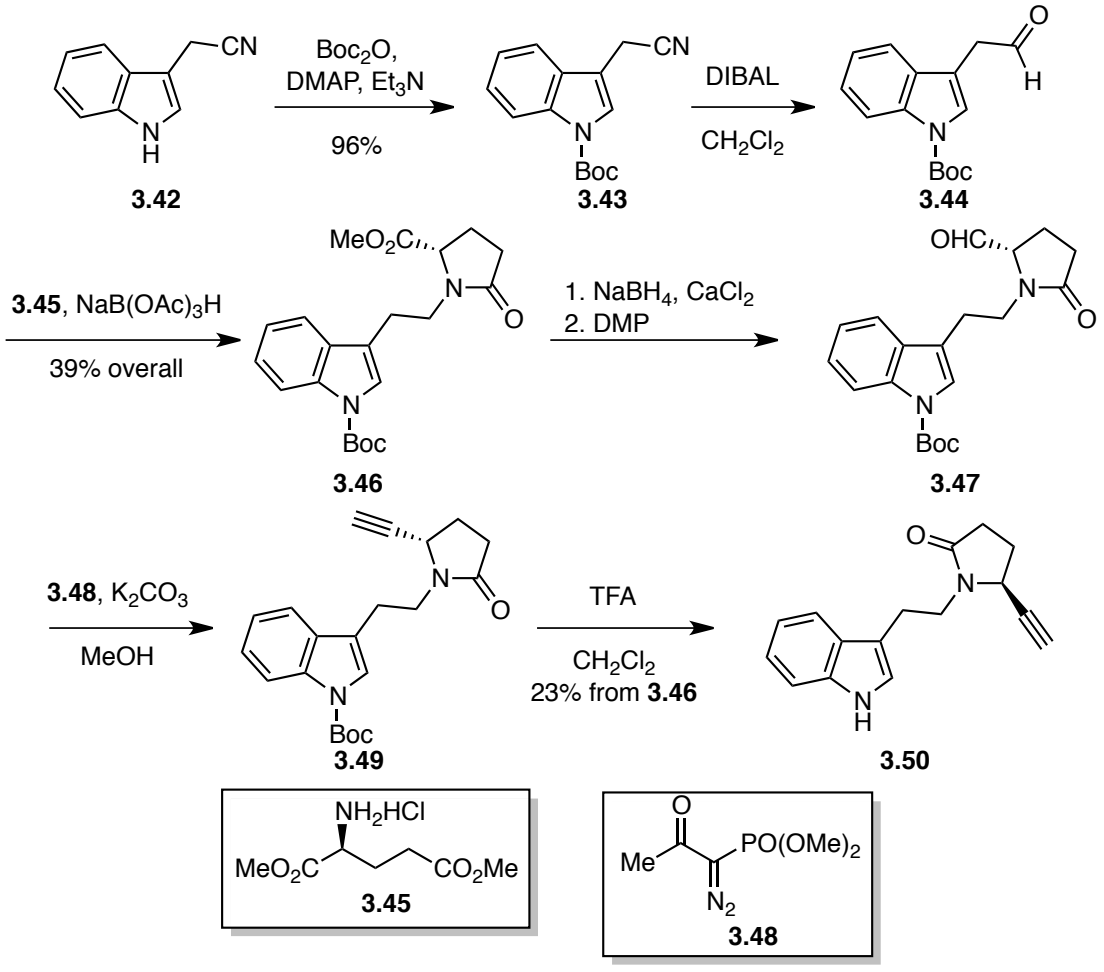


3.40 **3.41** **(3.1)**

Echavarren and coworkers reported a gold catalyzed cyclization to annelate eight membered rings at the 2,3-positions of indole.[191,192] The indole *N*-H of **3.42** was protected as its Boc derivative **3.43** in 96% yield (Scheme 3.5). Reduction of the nitrile of **3.43** to the aldehyde **3.44**, followed by reductive amination with **3.45** afforded the lactam **3.46** in

39% yield over the two steps. The ester moiety was reduced to the alcohol with $NaBH_4$ in the presence of $CaCl_2$,[193,194] and the alcohol was oxidized to the aldehyde **3.47** using Dess-Martin periodinane.[39] The aldehyde group of **3.47** was converted to the alkyne **3.49** with the Ohira-Bestmann[195,196] reagent **3.48**, and the Boc group was removed with TFA to deliver **3.50** in 23% yield from **3.46**. With **3.50** in hand, the gold catalyzed cyclization reaction was studied.

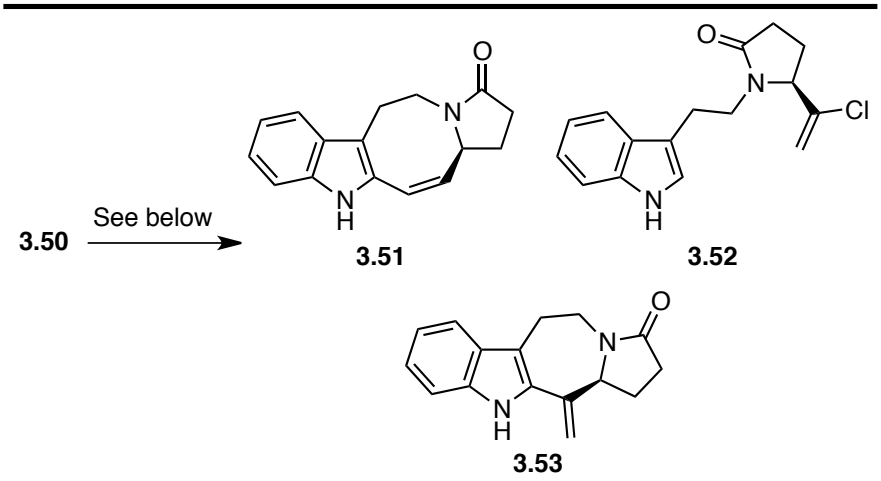
Scheme 3.5 Echavarren's synthesis of lactam **3.50**



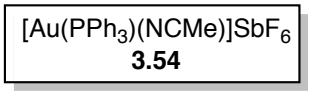
When **3.50** was exposed to a variety of catalytic gold species several products were obtained (Table 3.1). Unfortunately, the product ratio depended on the catalyst

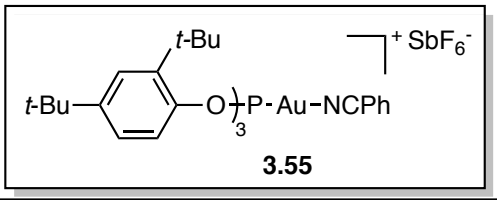
used. For example, when $AuCl_3$ was used, a mixture (95:5) of the desired product **3.51** and the side product **3.52** was obtained in a combined 55% yield (Entry 1). The side product presumably arose from the gold-catalyzed hydrochlorination of the alkyne. Employing AuCl as the catalyst provided **3.51** as the sole product in 42% yield (Entry 2). The neutral gold catalyst **3.54** delivered a mixture (78:22) of **3.51** and **3.53** (Entry 3), while the cationic gold catalyst **3.55** altered the regioselectivity of the cyclization by delivering a mixture (13:87) of **3.51** and **3.53** (Entry 4). Echavarren proposed that the reversal in regioselectivity upon cyclization is due to the different steric requirements between the neutral **3.54** and cationic **3.55** gold catalysts. This method is noteworthy in that the stereochemistry of the cyclization is consistent with what was proposed for the natural products in Figure 3.1; however, it is not apparent how **3.51** would be elaborated to any of these compounds. For example, installation of the cyclopropane-containing unit of the lundurines would require activation of the methine proton of **3.51**.

Table 3.1 Echavarren's approach to the tetracyclic core of the *Kopsia* alkaloids



Entry	Catalyst	Products (ratio)	Yield (%)
1	AuCl	**3.51**:**3.52** (95:5)	55
2	$AuCl_3$	**3.51**	42
3	**3.54**	**3.51**:**3.53** (78:22)	--
4	**3.55**	**3.51**:**3.53** (13:87)	--





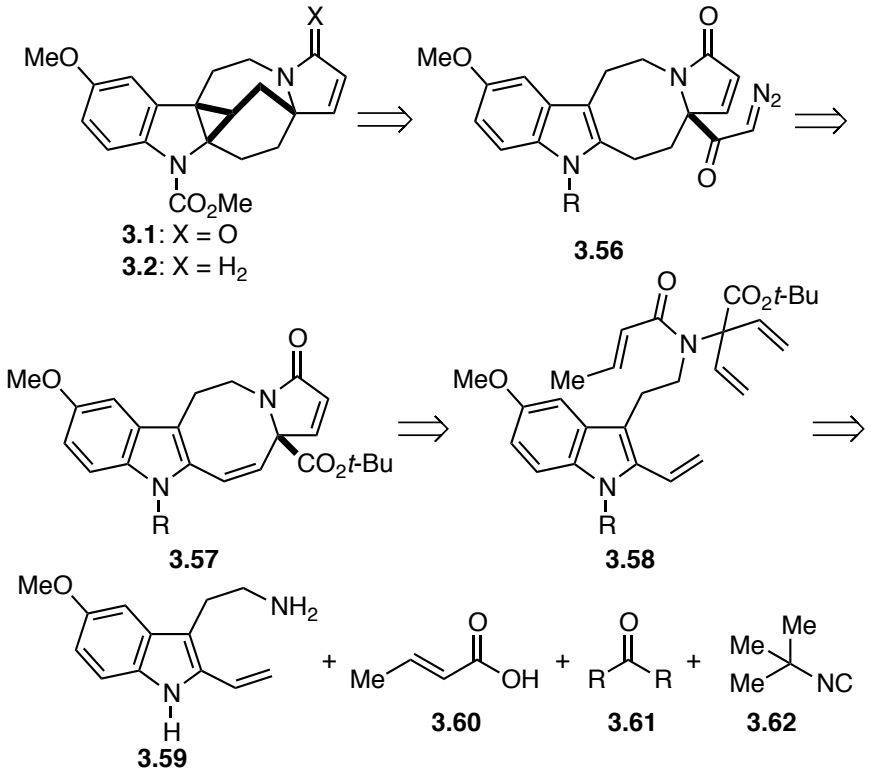
3.3 The Martin Group's Approach to the Lundurines

The Martin group has had a longstanding interest in the preparation of architecturally challenging indole alkaloids.[197-216] Of the many contributions the group has made to the field of total synthesis, the application of ring closing metathesis (RCM)[217,218] to the realm of natural products is of particular importance.[219-231] A plethora of natural products has succumbed to synthesis using RCM chemistry that would have been difficult to obtain otherwise, and it has opened the door to other elegant applications that were not foreseen at the time. We saw the synthesis of lundurines A-D (**3.1**-**3.4**) as a potential application of a novel RCM strategy (Scheme 3.6).

We initially envisioned a late stage copper catalyzed cyclopropanation[232-234] of the α-diazoketone moiety of **3.56** with the 2,3-positions of indole, expecting that cyclopropanation of the spirocyclic lactam would be disfavored due to ring strain.[235] The resulting cyclopropyl ketone would then be subjected to a selective Wolff-Kishner deoxygenation to deliver lundurine A (**3.1**).[236,237] Reduction of the lactam of **3.1** would deliver lundurine B **3.2**.[238] The α-diazoketone would be prepared from the *tert*-butyl ester **3.57** after saponification, formation of the acid chloride or mixed anhydride, and diazomethylation.[239,240] The olefin within the more electron rich eight-membered ring would undergo a selective hydrogenation rather than the olefin within the lactam. The pivotal step in the proposed synthesis was an enantioselective double RCM of the tetraene **3.58** to provide the tetracyclic core **3.57**.[241-245] While the RCM of two rings in a single transformation is known, the formation of a five- and eight-membered ring in a single reaction is unprecedented. The enantioselective aspect of the double RCM was also unprecedented at the time. Due to the inherent difficulty associated with the formation of eight-membered rings, this proposed reaction posed a significant synthetic challenge.[219,223,246]

The tetraene **3.58** would be obtained through a convergent Ugi multicomponent reaction[186] using tryptamine **3.59**, *trans*-crotonoic acid (**3.60**), ketone (**3.61**), and isocyanide **3.62**.[247] We envisioned that the R-groups of ketone **3.61** would serve as the masked vinyl groups of **3.58**, the isocyanide **3.62** would be hydrolyzed to the *t*-butyl ester at a later stage in the synthesis, and the Boc group would be installed after the Ugi reaction. With a proposed route to lundurines A and B (**3.1** and **3.2**) in hand, synthetic efforts began towards accessing amine **3.59**.

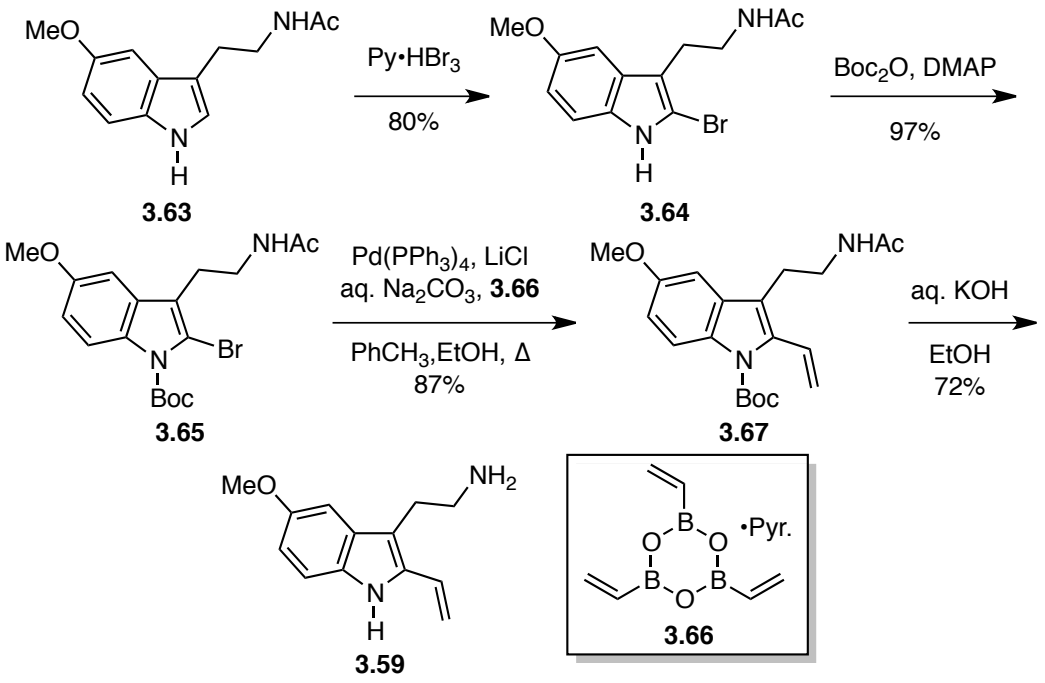
Scheme 3.6 A double RCM approach to lundurines A (**3.1**) and B (**3.2**).



3.3.1 Preparation of the indole amine

Tryptamine **3.63** was regioselectively brominated at the C(2) position with pyridinium tribromide to deliver **3.64** in 80% yield, and the indole *N*-H was protected as its Boc derivative **3.65** in 97% yield (Scheme 3.7). It was envisioned that both of the nitrogen atoms could be unmasked in a single reaction, thus the Boc group was chosen for this purpose. Other electrophilic brominating reagents resulted in poor yields and the formation of products having bromine on the benzene ring. A palladium-catalyzed Suzuki cross-coupling of the protected bromide with boronic anhydride **3.66** provided the 2-vinyl substituted indole **3.67** in 87% yield. Both of the protecting groups on the nitrogen atoms were then removed to provide **3.59** in 72% yield. The Ugi four-component coupling reaction was next investigated.

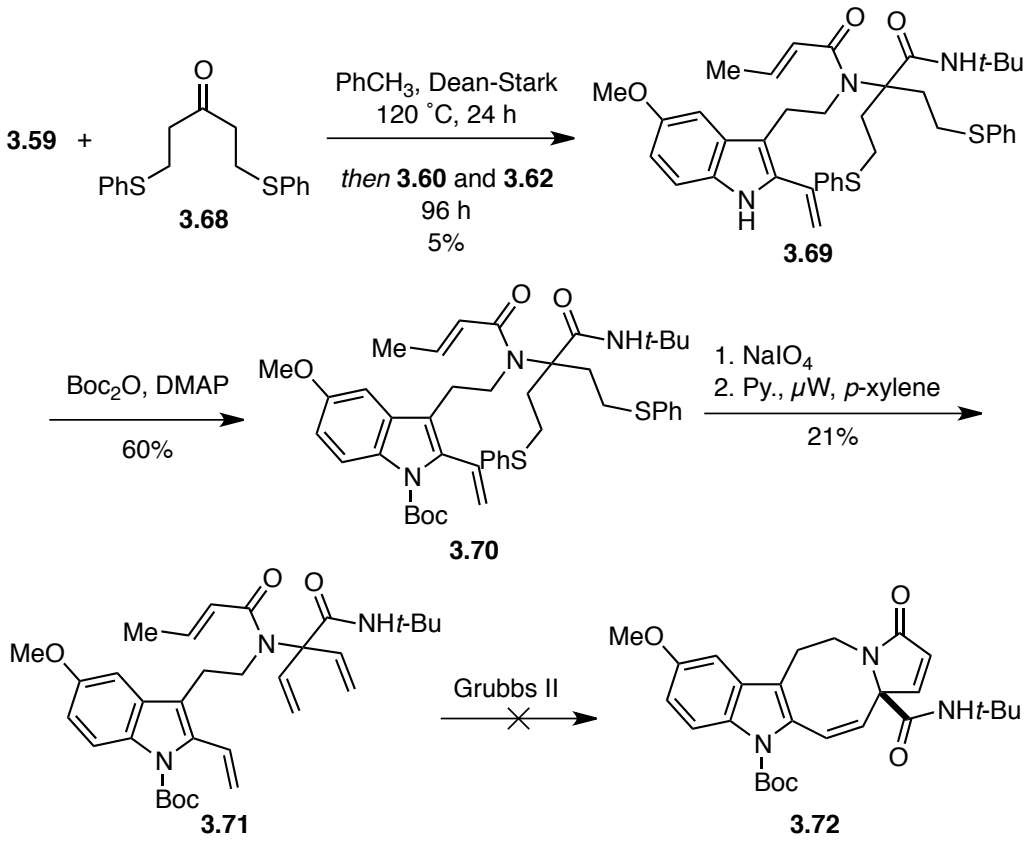
Scheme 3.7 Synthesis of the 2-vinyl substituted tryptamine



The imine formation between amine **3.59** and ketone **3.67** required elevated temperatures under Dean-Stark conditions (Scheme 3.8). After 24 h, acid **3.58** and isocyanide **3.60** were added, and the reaction was stirred for four days; however, Ugi product **3.68** was obtained in only 5% yield, while ketone **3.67** was recovered in 55% yield. This stepwise approach to the Ugi reaction was far from efficient; however, it did provide Dr. Orr with sufficient material to explore the double RCM reactions to the tetracyclic lundurine core. The indole *N*-H was protected as its Boc derivative **3.69** in 60% yield. The vinyl groups were unmasked by oxidizing the sulfur atoms to sulfoxides, and then eliminating the resulting phenylsulfoxide groups by heating in the microwave oven to provide **3.71** in 21% overall yield. The tetraene **3.71** was then exposed to Grubbs second generation metathesis catalyst with hopes of obtaining **3.72**, but instead a complex mixture of products was obtained. The starting material was recovered in 44% yield. Unfortunately, there was not a compound with spectral data consistent with the desired

tetracycle present after the reaction. The scale of the reaction was less than 1 mg, which made assigning structures to the side products difficult. Dr. Orr realized that the Ugi approach to the RCM precursor was not an effective route and sought an alternative strategy to the lundurines.

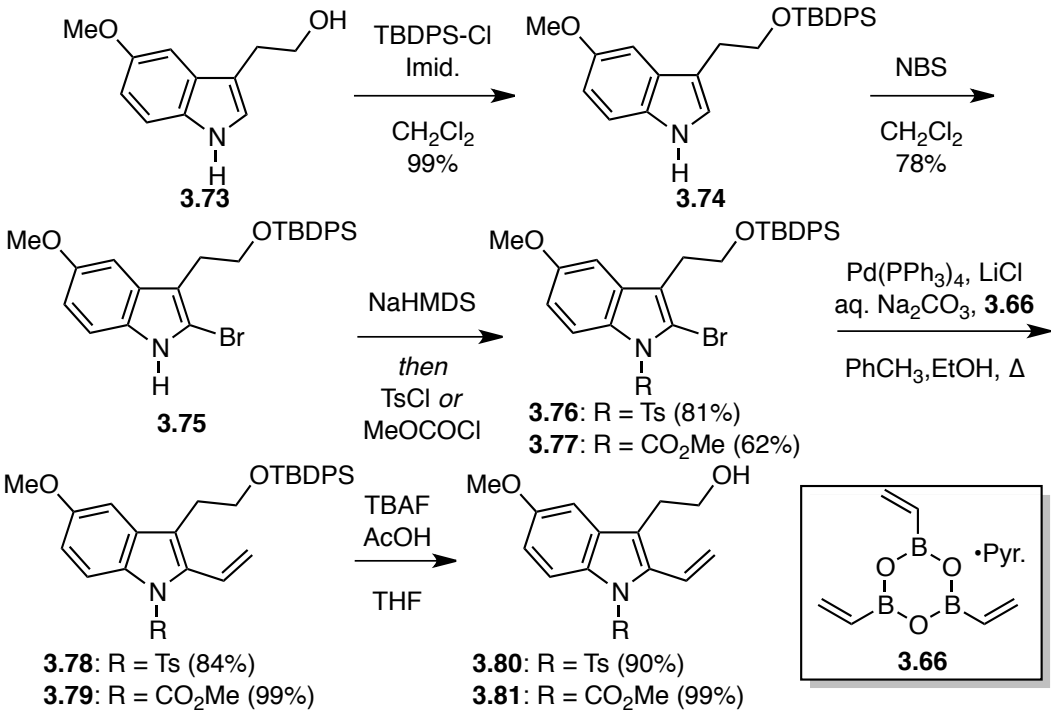
Scheme 3.8 The Ugi multicomponent reaction approach to the lundurines



Since an Ugi multicomponent reaction failed to prepare the tetraene, Dr. Orr queried whether a reductive amination would provide entry to the RCM precursors. The strategy was thus adjusted, and two indole alcohols that differ only in the substituent on the indole N-atom were prepared (Scheme 3.9). Future studies in the lundurine project saw the use of both protected indole derivatives. The alcohol group of commercially available 5-methoxytryptophol (**3.73**) was protected as its TBDPS ether **3.74** in 99%

yield. Regioselective bromination of the C(2) position of indole was accomplished with NBS to deliver **3.75** in 78% yield. Other electrophilic brominating reagents resulted in poor yields and the formation of products having bromine on the benzene ring. Deprotonation of **3.75** followed by reaction with *p*-TsCl or methyl chloroformate delivered **3.76** and **3.77** in 81% and 62% yields, respectively. A palladium-catalyzed, Suzuki cross-coupling of the protected bromides **3.76** and **3.77** with boronic anhydride **3.66** provided the 2-vinyl substituted indoles **3.78** and **3.79** in 84% and 99% yields, respectively. Finally, exposure of **3.78** and **3.79** to TBAF buffered with acetic acid delivered the alcohols **3.80** and **3.81** in 90% and 99% yields, respectively. The entire sequence provided gram quantities of material.

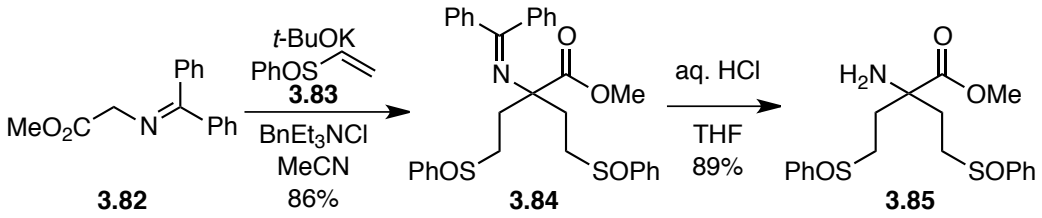
Scheme 3.9 Synthesis of the *N*-protected indole alcohols



The amine component required for the reductive amination approach would contain the masked divinyl substituent. The preparation of the amine **3.85** began by

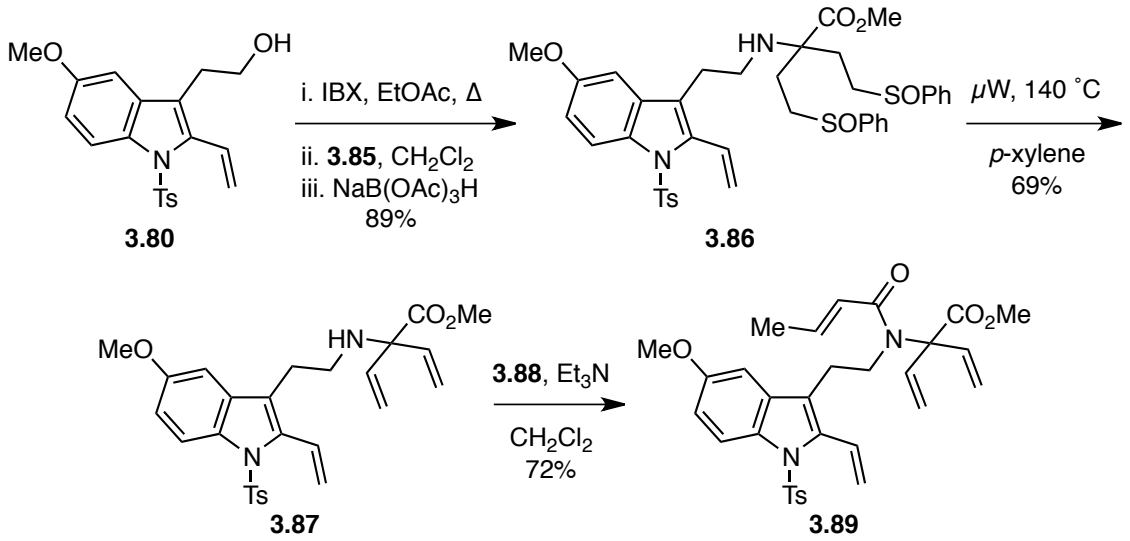
subjecting the imine **3.82**, which was formed upon the condensation of glycine with benzophenone, to a double Michael addition with phenylvinyl sulfoxide (**3.83**) in the presence of *t*-BuOK under phase transfer conditions to deliver **3.84** in 86% yield (Scheme 3.10). Use of K_2CO_3 as the base resulted in the formation of mono-alkylated material that was resilient to a second alkylation. The imine of **3.84** was hydrolyzed under acidic conditions to the amine **3.85** in 89% yield. The next phase of the synthesis involved coupling of **3.85** and tosyl-protected indole alcohol **3.80** by reductive amination.

Scheme 3.10 Synthesis of the amine **3.85**



Oxidation of the alcohol moiety of **3.80** to an aldehyde was achieved with IBX in EtOAc under reflux, and condensation of the aldehyde with **3.85** and subsequent reduction of the intermediate imine with $NaB(OAc)_3H$ delivered the secondary amine **3.86** in 89% overall yield (Scheme 3.11). The tosyl derivative **3.80** was used in place of the *N*-carbomethoxy indole because of concerns regarding the stability during some transformations in the synthetic sequence. The vinyl groups of **3.86** were unmasked by pyrolytic elimination of the phenylsulfoxide groups by heating in a microwave oven to deliver **3.87** in 69% yield. The amine was then acylated with *trans*-crotonoyl chloride (**3.88**) to furnish the crotonamide tetraene **3.89** in 72% yield. With tetraene **3.89** in hand, attention was focused on the crucial double ring closing metathesis to form the tetracyclic core of lundurines A (**3.1**) and B (**3.2**).

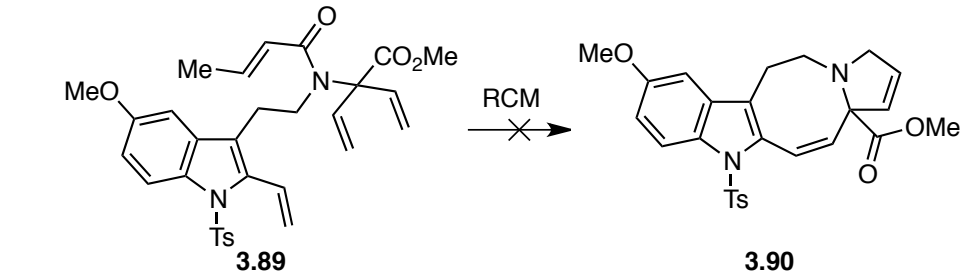
Scheme 3.11 Synthesis of the *N*-tosyl protected RCM precursor



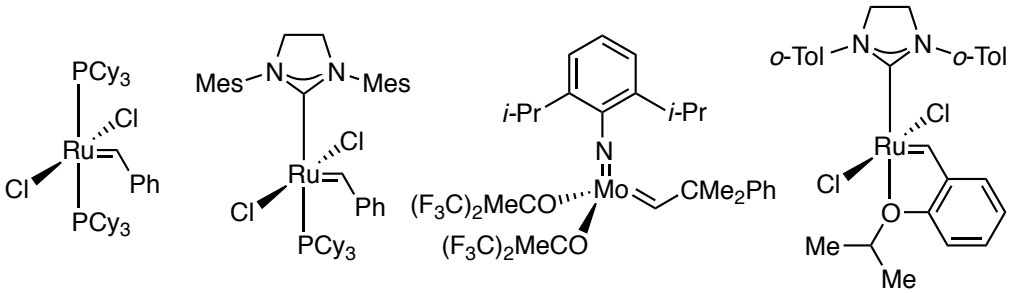
3.3.2 Attempted RCM of the tetraene

The initial set of conditions that were investigated used the first generation Grubbs catalyst **3.91** in CH_2Cl_2,[248] but none of the desired tetracycle **3.90** was observed (Scheme 3.12). Switching solvents to benzene and heating under conventional thermolysis or in the microwave oven at elevated temperatures also provided none of the desired product. The more reactive second-generation Grubbs catalyst **3.92** was also used, but it did not deliver the tetracyclic product **3.90**.[249] There was some evidence that a tricyclic product with an eight-membered ring was formed in low yield. The highly reactive Schrock catalyst **3.93** was next explored, but it failed to deliver the anticipated product.[250] Finally, the second generation Stewart-Grubbs catalyst **3.94** was used.[251] The catalyst is noted for its ability to catalyze the metathesis of sterically congested olefins because the *o*-tolyl substituents on the *N*-heterocyclic carbene can rotate to a less sterically encumbered conformation. However, this catalyst did not promote the double RCM.

Scheme 3.12 Unsuccessful double RCM to the tetracycle

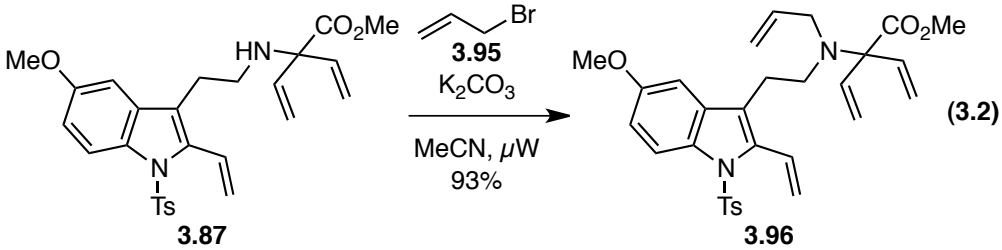


3.89 **3.90**



Grubbs I **3.91** | Grubbs II **3.92** | Schrock **3.93** | Stewart-Grubbs II **3.94**

Attention was then turned to lundurine B (**3.2**) as the target, hoping that a less sterically hindered olefin in the tetraene would facilitate metathesis (Equation 3.2). To this end, **3.96** was prepared in 93% yield by allylation of **3.87** with allyl bromide (**3.95**) in the microwave oven at 80 ˚C. With the allylated amine in hand, the double RCM was next explored.

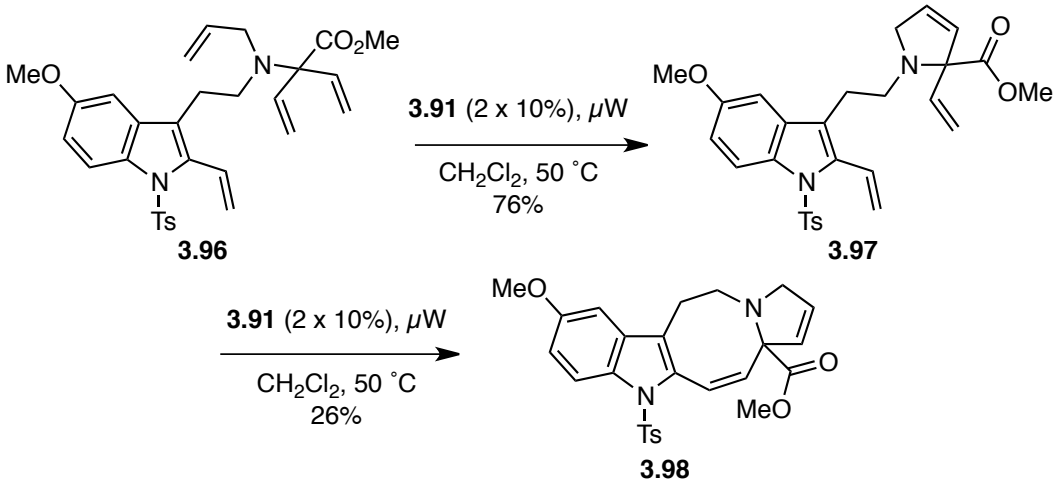


3.87 **3.96** **(3.2)**

In the event, exposure of **3.96** to a variety of ruthenium catalysts delivered the monocyclized product **3.97** (Scheme 3.13). This was welcomed news because the formation of **3.97** was not observed using the crotonamide derivative **3.89**. The monocyclized product **3.97** could be isolated in yields up to 76% using the first

generation Grubbs catalyst **3.91**. There were two important lessons that were learned with this tetraene: the first generation Grubbs catalyst proved superior to the other catalysts shown in Scheme 3.10, and reactions performed in the microwave oven provided the shortest reaction time, highest yields, and cleanest reaction mixtures. Gratifyingly, exposure of **3.97** to a second round of the first generation Grubbs catalyst in the microwave oven at reflux and then stirring at ambient temperature provided a product that was tentatively assigned the structure of **3.98** in 26% yield. Dr. Orr assigned the structure of **3.98** based on NMR spectral data and HRMS. The NMR spectrum of **3.98** was not clean due to the presence of side products in the reaction and the small amounts of material available for analysis; however, the HRMS provided a *m/z* consistent with that of **3.98**. Attempted optimization of the reaction by increasing catalyst loadings and reaction times led to no improvement. Formation of the hydrochloride salt of the amine, which is reported to inhibit any interaction the amine has with the ruthenium atom of the catalyst, did not increase the yield of the reaction.[252] The reaction could be streamlined into a one-pot process, but this led to poor yields of the putative tetracycle **3.98**.

Scheme 3.13 Synthesis of the proposed tetracyclic core of lundurine B (**3.2**) by RCM



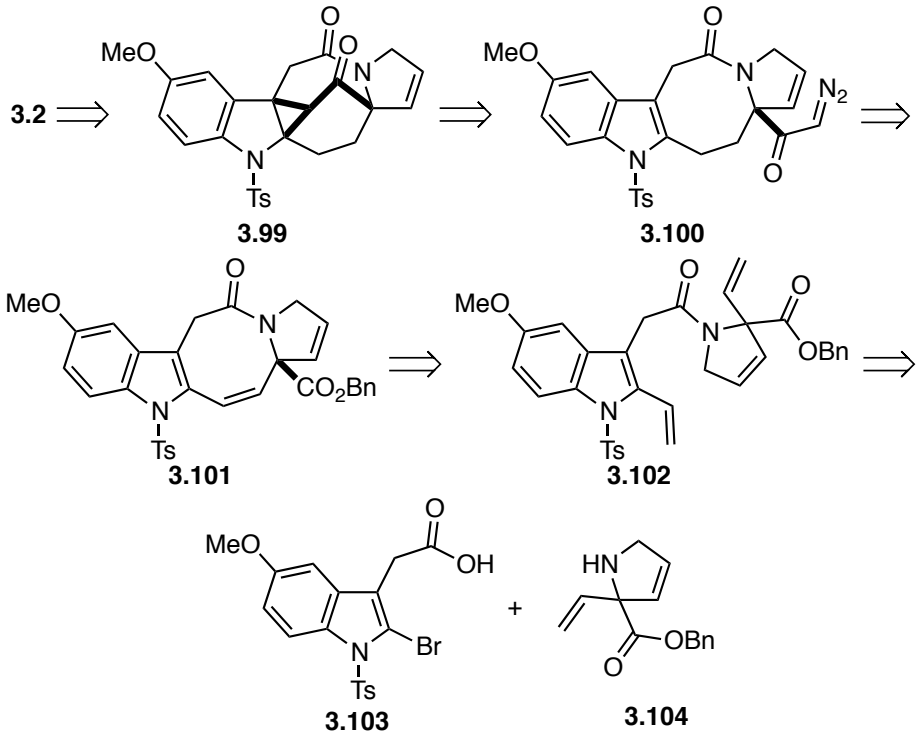
It was at this time Dr. Jianhua Tian took over the project. He suspected there was a problem with the amine portion of the tetraene **3.96** evident by the problematic metathesis reaction. Nitrogen atoms are known to inhibit metathesis by coordinating to the ruthenium atom.[253] Dr. Orr attempted to prevent this chelation by making the HCl salt of the amine tetraene. Unfortunately, this was unsuccessful and the tetracycle was not obtained. Dr. Tian decided to begin his investigation of the synthesis of lundurine B by preparing an amide-containing tetraene.

3.4 Alternative Entry to the Synthesis of the Lundurines

3.4.1 Application of an amide tetraene

Rather than the crotonamide that was prepared in Scheme 3.14, the carbonyl moiety of the amide that Dr. Tian envisioned would be located within the eight-membered ring after the double RCM. Lundurine B (**3.2**) is expected to arise from **3.99** after a one-pot deoxygenation of the ketone and amide. The remaining steps in the retrosynthesis would then be similar to the first generation route. A late stage cyclopropanation by the α-diazoketone of **3.100** would deliver the hexacyclic core, and the diazo group would be installed after functionalization of the benzyl ester of **3.101**. An RCM was proposed for the formation of the tetracycle **3.101**. The tetracycle was expected to arise from the tetraene **3.102**, which would be derived from a coupling between the carboxylic acid **3.103** and secondary amine **3.104**.

Scheme 3.14 Second generation retrosynthesis of lundurine B (**3.2**)

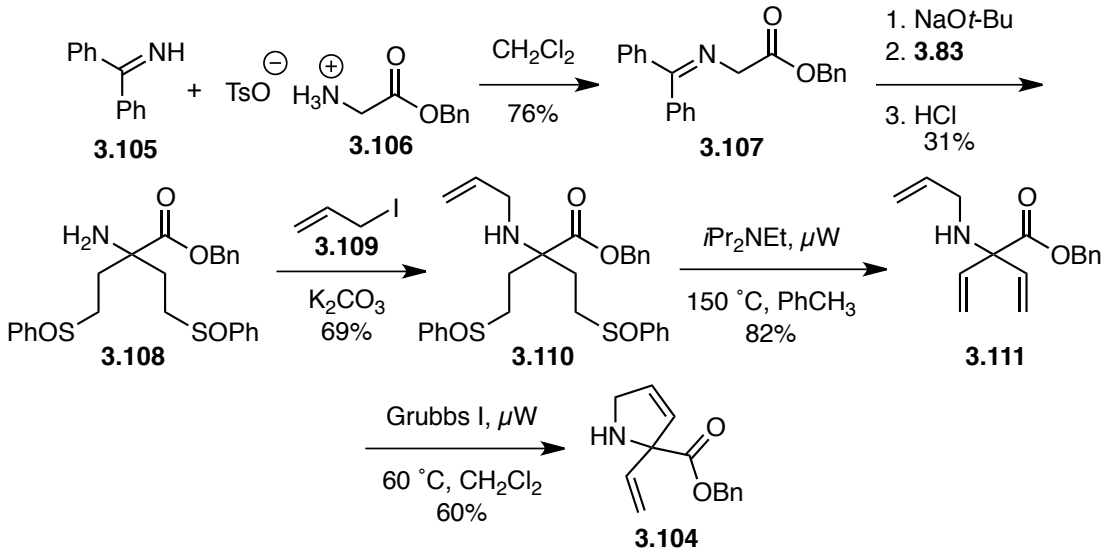


Dr. Tian proposed to use amine **3.104** rather than **3.85** for two reasons. The first concerns the use of a benzyl ester rather than a methyl ester. The benzyl ester was chosen because the methyl ester was difficult to saponify in early model studies of the route. The second reason dealt with making a structural change was to the amine itself. Since the structurally similar crotonamide **3.89** was unwilling to undergo metathesis, Dr. Tian queried whether bringing in an amine with one ring pre-formed would enable closure of the final eight membered ring due in part to the less sterically crowded environment around the vinyl group.

Preliminary efforts were focused on preparing amine **3.104** (Scheme 3.15). Stirring **3.105** with glycine benzyl ester *p*-toluenesulphonate salt (**3.106**) delivered the desired imine **3.107** in 76% yield. The Michael addition of **3.107** with phenylvinyl sulfoxide (**3.83**), followed by unmasking of the imine under acidic conditions gave the

amine **3.108** in 31% overall yield. The allylation of **3.108** with **3.109** provided the secondary amine **3.110** in 69% yield. The vinyl groups were unmasked upon heating in the microwave oven at 150 ˚C to provide **3.111** in 82% yield. Finally, exposing **3.111** to Grubbs first generation catalyst **3.91** delivered the dehydroproline derivative **3.104** in 60% yield.

Scheme 3.15 Synthesis of the amine benzylester **3.104**

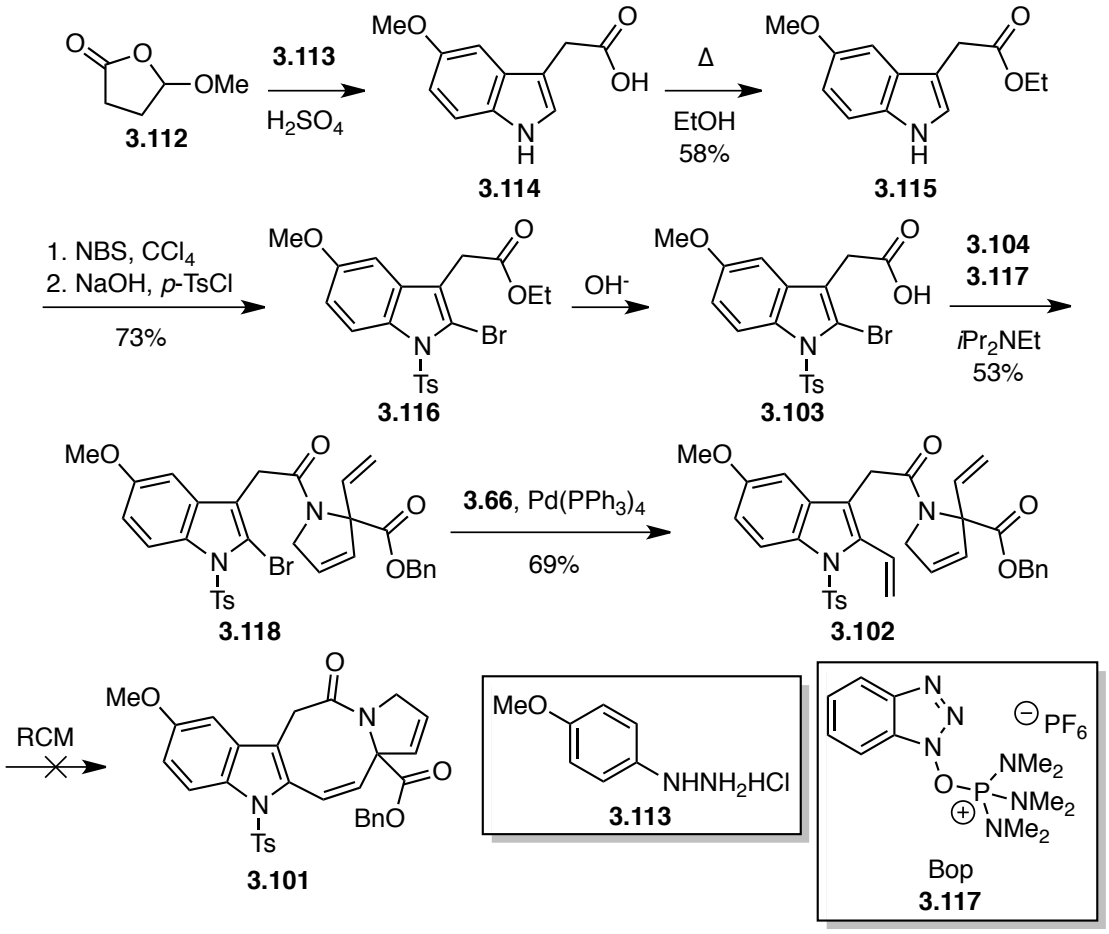


The synthesis of the requisite indole acetic acid **3.103** began with the Fisher indole synthesis of **3.112** with hydrazine **3.113** to provide the indole carboxylic acid **3.114** (Scheme 3.16). Heating a solution of **3.114** under reflux in EtOH provided the ethyl ester **3.115** in 58% overall yield. The C(2) position of indole was brominated with NBS, and the indole *N*-H atom was protected as its tosylate **3.116** in 73% overall yield. The tosylate protecting group was chosen because Dr. Tian sought to prepare a substrate that was similar in structure to that of Dr. Orr's substrate. The ester moiety was then saponified to the carboxylic acid **3.103** in an unrecorded yield. With **3.103** and **3.104** in

hand, Dr. Tian began to study the coupling of the amine and subsequent ring closing reactions.

Coupling of **3.103** and **3.104** was achieved using (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (**3.117**) in 53% yield. Installation of the vinyl group proceeded under standard palladium-catalyzed conditions to deliver **3.102** in 69% yield. Exposure of **3.102** to Grubbs II in the microwave oven for 3 h resulted in the quantitative recovery of starting material. In a second attempt, chlorodicyclohexyl-borane was added to the RCM. This Lewis acid is believed to suppress any potential chelate formation between the ruthenium carbene and a Lewis basic site within the molecule.[254] Unfortunately, there was no metathesis to the tetracycle **3.101** even at elevated temperatures (55-65 ˚C), and **3.102** was recovered in 70% yield. In the third and final attempt, the metathesis was performed with Grubbs II in the microwave oven in $PhCH_3$ for five hours, but no observable reaction occurred, and starting material was recovered.

Scheme 3.16 Unsuccessful RCM approach with amide **3.101**



3.5 SUMMARY AND CONCLUSIONS

The Martin group approach to the lundurines features a novel, enantioselective double RCM to form a five- and eight-membered ring in a single operation. Using an Ugi multicomponent reaction to prepare a tetraene was unsuccessful; however, a reductive amination approach provided facile access to a double RCM precursor. The double RCM of a tetraene delivered a product that Dr. Suvi Orr assigned to be the tetracycle **3.98**, an assignment that would later be shown as incorrect. Realizing there were low yielding sequences in the first generation route, Dr. Jianhua Tian proposed an alternative route in which a tetracycle would be obtained after only one ring closure (refer to Scheme 3.14).

After extensive studies with the amide RCM precursor **3.102**, the tetracycle **3.101** still remained elusive.

A revised synthesis of the lundurines was thus needed, one in which the difficulties with the previous routes would be addressed. The major problem encountered with the prior attempts to the lundurines was the double RCM. During the course of these studies, we believed that the major factor that prevented formation of the eight-membered ring was the sterically congested environment in which the ruthenium catalyst is expected to load. Thus a new tetraene with more favorable steric properties was sought.

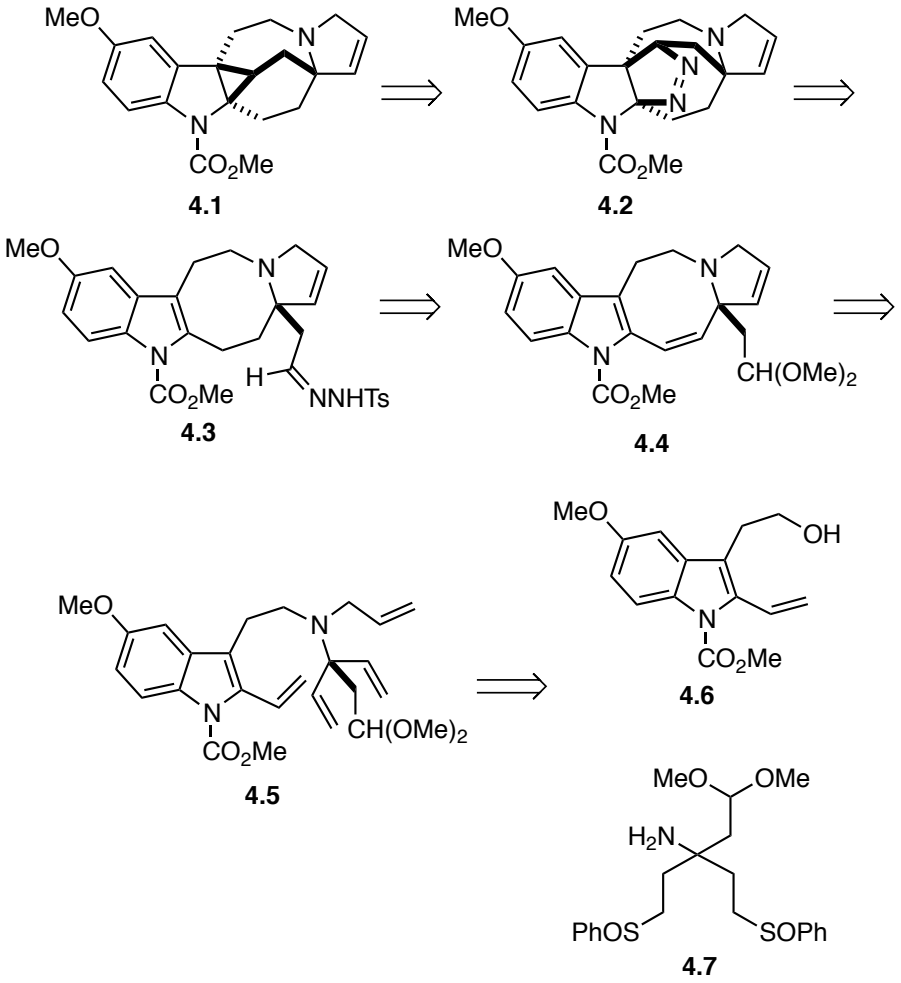
Chapter 4: Efforts Toward the Total Synthesis of Lundurine B

4.1 Revised Retrosynthesis to Lundurine B

Since the previous attempts made toward the synthesis of lundurine B (**4.1**) were unsuccessful, a revised route was devised. The new route would address the two problematic reactions that prevent the preparation of lundurine B (**4.1**) discussed in the preceding chapter. We needed a strategy by which the cyclopropane ring would be attached to the indole 2,3-positions without having to form the α-diazoketone. The new strategy would also involve preparing a double RCM substrate with more favorable steric and electronic properties that would enable us to access the tetracyclic core of lundurine B (**4.1**) in a more efficient manner.

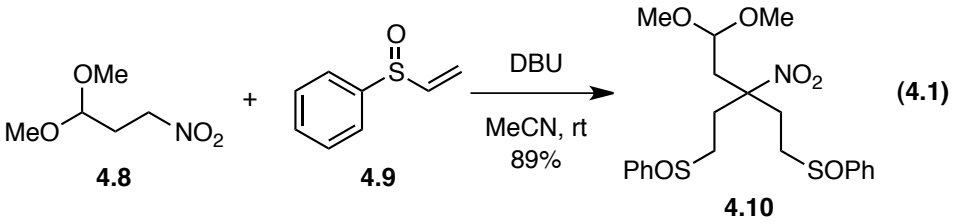
The revised retrosynthesis of lundurine B (**4.1**) is shown in Scheme 4.1. Lundurine B is expected to arise from the photo or thermal extrusion of nitrogen gas from pyrazoline **4.2**, which would be available from the [3+2] dipolar cycloaddition of tosyl hydrazone **4.3** across the 2,3-double bond positions of indole.[255-259] The *N*-tosylhydrazone is expected to arise from the reaction of *N*-tosylhydrazide with an aldehyde, which would be obtained from the acetal **4.4** upon acid catalyzed hydrolysis. The olefin in the eight-membered ring would be regioselectively hydrogenated over the olefin within the five-membered heterocycle based on prior precedent.[260,261] Tetracycle **4.4** is the product of a double RCM of the tetraene **4.5**, which is accessible from the reductive amination of alcohol **4.6** with the amine **4.7** after *N*-allylation and sulfoxide elimination. Indole **4.6** is available in five steps from commercially available material (*cf.* Scheme 3.9) while amine **4.7** requires a *de novo* synthesis. Herein describe our efforts to access the lundurine family of natural products and specifically lundurine B (**4.1**).

Scheme 4.1 Revised retrosynthesis of lundurine B featuring pyrazoline formation



Since the preparation of indole **4.6** was discussed in the preceding chapter, preliminary efforts were focused on the synthesis of amine **4.7** (Scheme 4.2). Following a procedure developed by Ono and coworkers,[262,263] nitroacetal **4.8**, which is available in two steps from acrolein, and commercially available phenyl vinyl sulfoxide (**4.9**) were mixed in the presence of DBU in MeCN. The acetal **4.10** was isolated in 89% yield after an acidic workup (Equation 4.1).

4.1.1 Preparation of the acetal amine

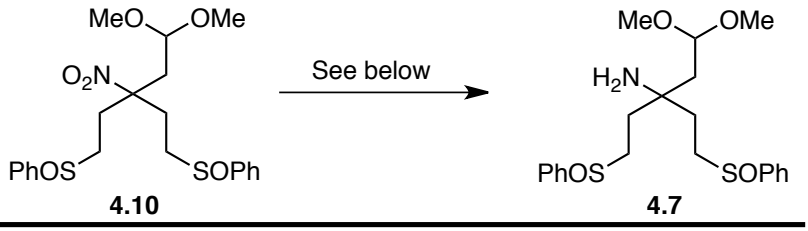


In his preliminary work with the new route, Dr. Tian exposed **4.10** to various reagents (Entries 1-4) with the hopes of inducing the chemoselective reduction of the nitro group to the amine in the presence of two sulfoxides (Table 4.1, Entries 1-4). Unfortunately, he obtained mixtures of products that he believed were the hydroxylamine **4.11** and sulfide **4.12**. Masses consistent with both compounds were present by LC-MS. Unfortunately, none of the desired amine **4.7** was observed in the crude reaction mixture by LC-MS or ^{1}H NMR spectroscopy.

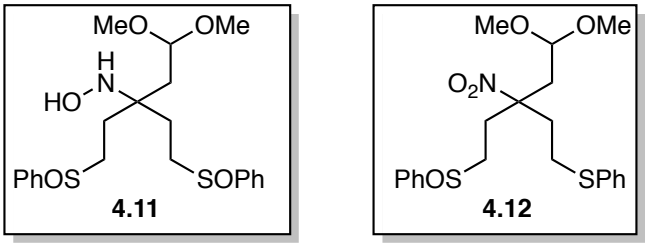
Next, we focused our attempts on using a metal hydride instead of hydrogen gas as the reducing agent. Treating **4.10** with either LAH, Cu-H, or $Zn(BH_4)_2$ resulted in decomposition of the starting material (Table 4.1, Entries 5-7). There was no indication of amine **4.7** in the crude product mixture, but masses consistent with **4.11** and **4.12** were present as indicated by LC-MS. Ni-H, prepared *in situ* from $NiCl_2$ and $NaBH_4$, gave the first positive result for this reaction, and the amine **4.10** was obtained in <32% yield (Entry 8).[264] Gratifyingly, zinc granules and NH_4Cl in MeOH under reflux provided the amine in 88% yield after column chromatography (Entry 9).[265] After further exploration of the reaction, we found that the hydroxylamine **4.11** made up the remaining mass balance. The hydroxylamine could be separated from the product and resubjected to the reduction reaction to obtain more of the amine. Prolonged reaction times or reaction temperatures above the boiling point of MeOH resulted in complete over reduction of the

sulfoxides to the sulfides. Careful monitoring of this reaction by TLC was required for reproducible results. This remarkable reduction provided us with significant quantities of the amine, which enabled us to carry on with the synthesis to the tetraene needed for the RCM.

Table 4.1 Successful reduction of the nitro group to the amine



Entry	Conditions	yield of **4.7** (%)
1	Pd/C, H_2, NH_4CO_3	RSM
2	Sn, AcOH	SP
3	Pd/C, H_2, AcOH	RSM
4	PtO_2, H_2	RSM
5	LAH, Et_2O	dec.
6	$CuOAc_2$, $NaBH_4$	dec.
7	$Zn(BH_4)_2$•Py	dec.
8	$NiCl_2$, $NaBH_4$, MeOH	32
9	Zn, NH_4Cl, MeOH, Δ	88

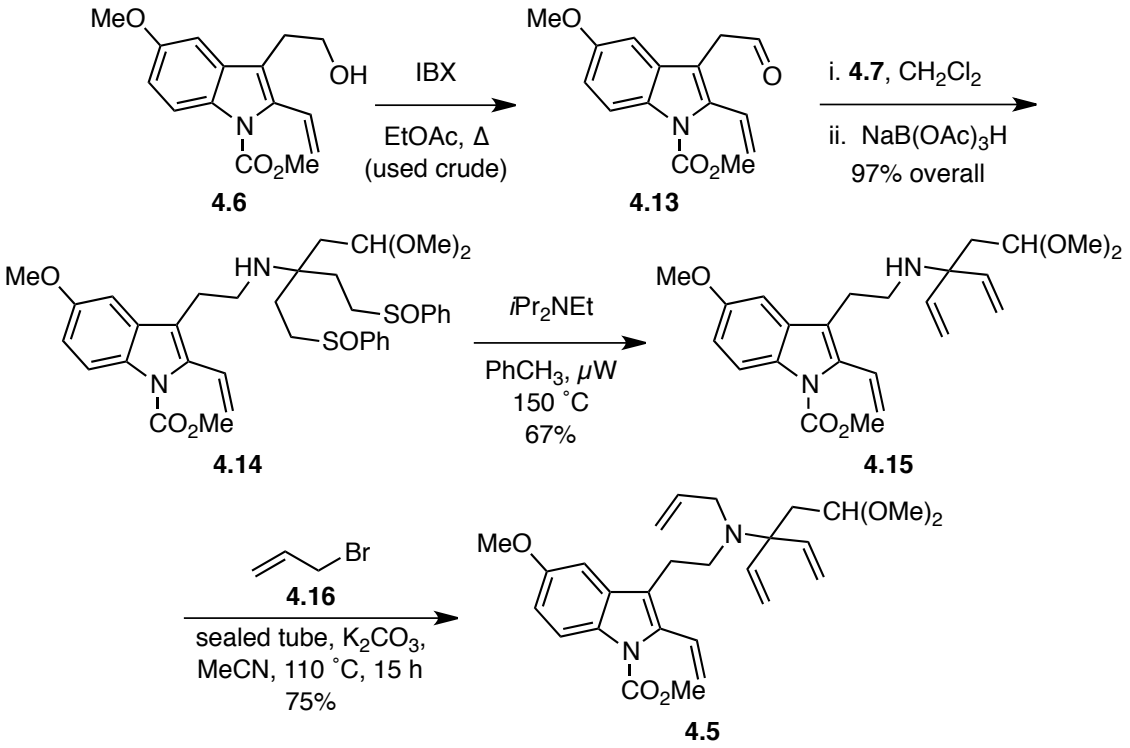


4.1.2 Synthesis of the *N*-methylcarbamate tetraene and RCM

The alcohol moiety of **4.6** was oxidized to the unstable aldehyde **4.13** with excess IBX in EtOAc under reflux (Scheme 4.2). The crude aldehyde **4.13** was condensed with **4.7**, and the resulting imine was reduced with $NaB(OAc)_3H$ to give amine **4.14** in 97% yield from **4.6**. The mixture was treated with excess *i*Pr_2NEt in $PhCH_3$ in a microwave

oven at 150 ˚C to generate triene **4.15** in 67% yield. The secondary amine was then allylated with allyl bromide (**4.16**) in a sealed tube to provide tetraene **4.5** in 75% yield. When the allylation was performed with microwave heating, the yields of **4.5** were inferior. With the tetraene in hand the pivotal double RCM was next investigated.

Scheme 4.2 Preparation of the *N*-methylcarbamate protected tetraene



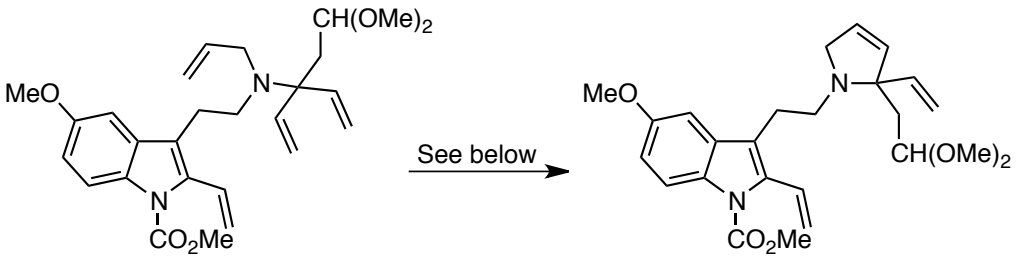
In the event, exposure of **4.5** to Grubbs I catalyst under microwave irradiation in CH_2Cl_2 afforded only the tricycle **4.17**; none of the desired tetracycle **4.4** was observed by LC-MS or ^{1}H NMR spectroscopy (Entry 1, Table 4.2). The reaction scale was insufficient for column chromatography, so the product distribution was analyzed by LC-MS. On a larger scale and under conventional heating, tricycle **4.17** was obtained in 59% yield (Entry 2). Upon switching to the more reactive Grubbs II catalyst, tricycle **4.17** was isolated in a lower 44% yield, but the reaction was only stirred at room temperature

(Entry 3). The remaining mass balance for this reaction was recovered starting material. It has been reported that Lewis basic functional groups such as amides and carbamates can chelate the active ruthenium species and slow down or even inhibit the RCM altogether.[253,266] This is an especially significant problem if five- or six-membered ring chelates are possible. A common solution is to add a Lewis acid such as $Ti(O\textit{i}Pr)_4$ to the reaction before the catalyst is added. It is believed that the Lewis acid prevents the catalyst/Lewis basic functional group chelate from forming and allows the catalyst to close the desired ring and dissociate from the product.[266,267] When a substoichiometric amount of $Ti(O\textit{i}Pr)_4$ was used in the RCM of **4.5** with Grubbs I (Entry 4), the reaction only provided a 50% yield of **4.17** and none of the desired tetracycle. Screening various solvents and temperatures with the additive did not remedy the problem.

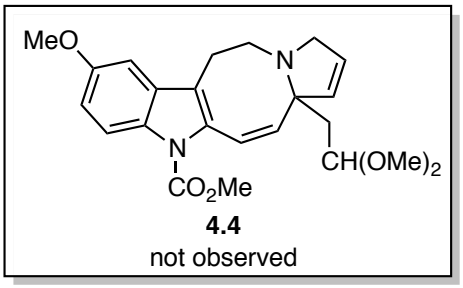
Other reports by Grubbs indicate that the second generation Grubbs-Hoveyda catalyst (G-H II) is a superior catalyst for the formation of five-, six- and seven-membered rings.[268] In the same publication, Grubbs also reported that $PhCH_3$ and methyl *tert*-butyl ether (MTBE) are superior solvents compared to CH_2Cl_2 in terms of reaction rate and yield for this type of ring closure. With this information in hand, we next screened the Grubbs-Hoveyda second-generation metathesis catalyst with both solvents. In both cases (Entries 5 and 6), only recovered starting material was obtained from the reaction. The solvent perfluorotoluene (C_7F_8) is reported to have a beneficial effect on the rate of RCM reactions that are known to be sluggish when run in traditional RCM solvents such as CH_2Cl_2 or benzene.[269] The electron deficient solvent is believed to coordinate to and stabilize the 14-electron ruthenium complex after ligand dissociation. It was reported that the longer lifetime of the active ruthenium catalyst allows more facile olefin coordination and thus faster catalytic turnovers. The use of C_7F_8 as a solvent is best applied to Grubbs catalysts with aromatic ligands such as Grubbs II and G-H II.

When the solvent was applied to our system (Entries 7 and 8), the reaction did proceed faster relative to Entries 1 and 2, but the tetracycle was still not obtained. In addition to the conditions shown in Table 4.2, we also screened a variety of other ruthenium catalysts, nontraditional solvents, temperatures, reaction times, catalyst loadings, reaction concentration, methods by which the catalyst was added, etc. all of which led to either recovery of the starting tetraene, formation of the undesired tricycle, and/or formation of intractable mixtures of products.

Table 4.2 Attempted double RCM with the tetraene **4.5**



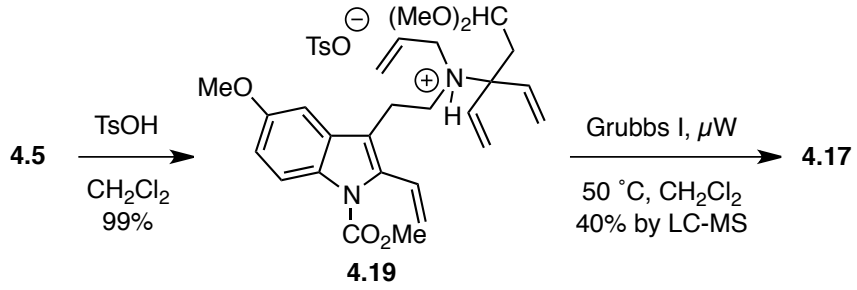
Entry	Catalyst	Loading (%)	Solvent	Conditions	Yield of **4.17** (%)
1	Grubbs I	25	CH_2Cl_2	μW, 50 ˚C, 4 h	--
2	Grubbs I	20% x 2	CH_2Cl_2	Δ, 96 h	59
3	Grubbs II	20	CH_2Cl_2	120 h, rt	44
4	Grubbs I	10	CH_2Cl_2	$Ti(OiPr)_4$ (30%), rt	50 + 20 RSM
5	G-H II	10	$PhCH_3$	rt - Δ	RSM
6	G-H II	10	MTBE	rt - Δ	RSM
7	Grubbs II	10	C_7F_8	rt then μW	40 (LC-MS)
8	G-H II	10	C_7F_8	μW, 70 ˚C	50 (LC-MS)



4.4
not observed

As mentioned earlier, Lewis basic functional groups can shut down the RCM reaction by coordinating to the ruthenium atom. Basic nitrogen atoms have also been known to chelate the ruthenium catalyst after ligand dissociation.[253,267] While tertiary amines are not as likely to prevent metathesis compared to primary amines, we queried whether the amine was preventing metathesis of the second ring. To rule out any potential influence the amine could have on the reaction, the salt of the amine was prepared (Scheme 4.3). Formation of the HCl salt was surprisingly challenging, and low yields of the salt were obtained; however, attempted RCM of the HCl salt of **4.5** resulted in complete decomposition of the starting material with no identifiable product. Tosylate salts of amines are reported to be superior to HCl salts under certain metathesis conditions.[253] Thus, treating amine **4.5** with anhydrous *p*-toluenesulphonic acid provided a quantitative yield of the amine salt **4.18**. Unfortunately, heating this salt in the presence of Grubbs I in the microwave oven only provided a mixture (2:3) of **4.17** and starting material; no tetracycle was observed even at higher temperatures.

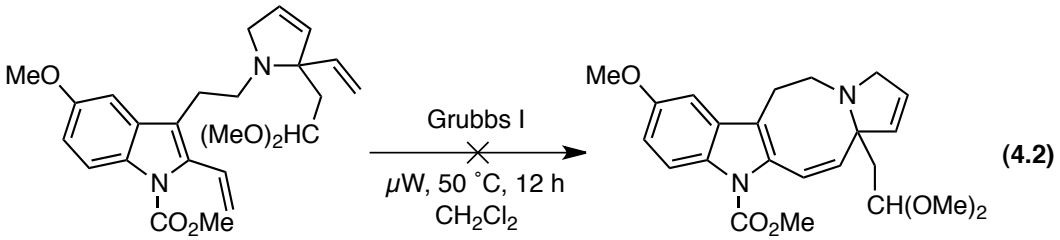
Scheme 4.3 Double RCM of the tosylate salt of amine **4.5**



4.1.2.1 Alternative approaches to the N-methylcarbamate tetracycle

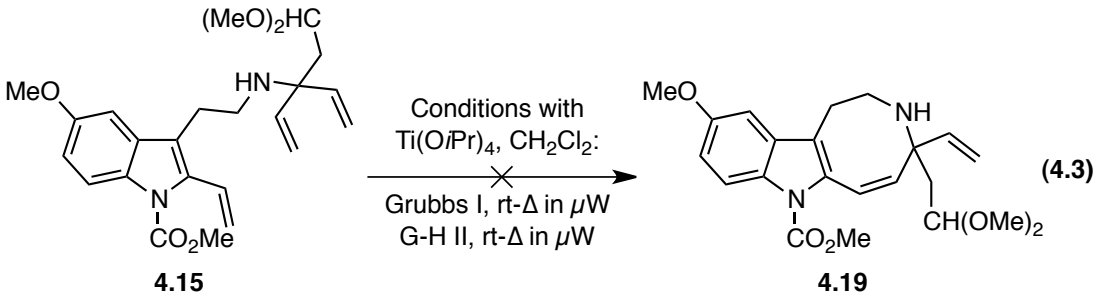
Since the double RCM of **4.5** was unsuccessful and the formation of the tricycle occurred in good yield, we next tried a stepwise approach. Our thinking was that with the five membered ring already formed, the catalyst would have to load onto the vinyl olefin

to form the eight-membered ring. Under the conditions of the first RCM, there may have been a contaminant from the catalyst that prevented successful loading onto one of the remaining olefins. Grubbs has reported that ruthenium catalyst decomposition products can cause undesired side reactions, such as olefin isomerizations, after the metathesis has occurred.[270] In the event, subjecting the tricycle to the first generation Grubbs catalyst resulted in the isolation of only starting material (Equation 4.2). A compound with mass consistent with the tetracycle was not observed in the LC-MS. Since the purification of **4.17** required multiple columns, we no longer felt this was a worth pursuing further.



4.17 **4.4** **(4.2)**

We next decided to try to form the eight-membered ring of **4.19** first by exposing triene **4.15** to the RCM (Equation 4.3). Two equivalents of Ti(O*i*Pr)$_4$ were also used in the reaction to suppress chelation of the catalyst with the methylcarbamate and the basic amine. Surprisingly, only starting material was recovered from the reaction in both cases. The stubbornness of the eight-membered ring forming reaction could be due to a number of factors, such as the chelation problems, the sterically crowded environment around the neopentyl olefin which the catalyst is expected to load onto, or the inherent difficulty associated with forming eight- and nine-membered rings compared to five, six, seven and larger sizes.[246] With these unfortunate experiences behind us, we felt it was time to change the plan.

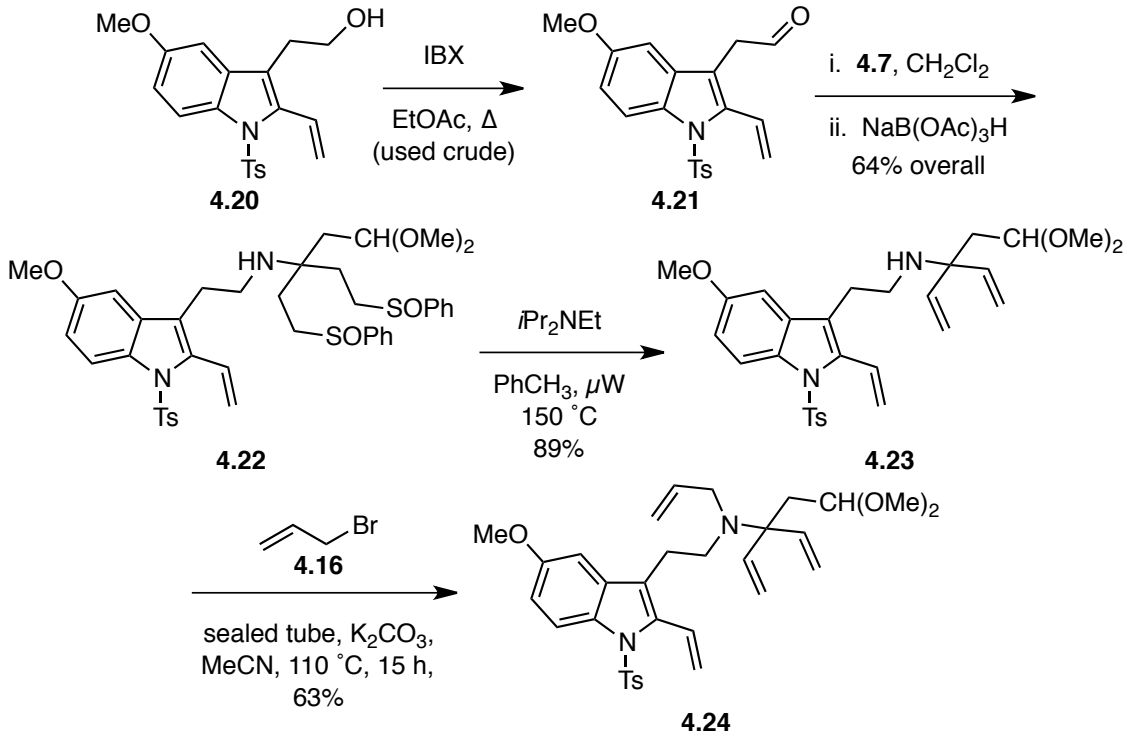


4.15 **4.19** **(4.3)**

4.1.3 Synthesis of the *N*-tosyl tetraene and RCM

In the first generation synthesis toward lundurine B (**4.1**), Dr. Suvi Orr isolated a compound that she assigned to be a tetracycle (*cf*. Scheme 3.15). The double RCM precursor contained an *N*-tosyl protecting group rather than an *N*-methylcarbamate.[235] Accordingly, our next course of action was to incorporate an *N*-tosyl group on the tetraene. Although removing the methylcarbamate from indole **4.5** was simple, attaching the tosyl group was not possible. We were thus forced to start from the beginning by preparing *N*-tosylindole **4.20** in five steps adapting the known procedure (*cf*. Scheme 3.9). Reductive amination of **4.20** with acetal amine **4.7** provided secondary amine **4.22** in 64% overall yield. Elimination of the sulfoxides using microwave heating provided **2.23** in 89% yield, and allylation of **4.23** to **4.24** occurred in 63% yield upon reacting with **4.16** in a sealed tube. With *N*-tosyl tetraene **4.24** in hand, the double RCM was explored.

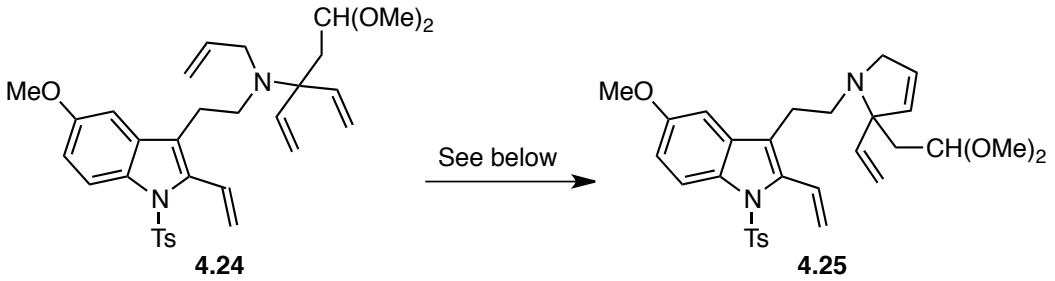
Scheme 4.4 Synthesis of the *N*-tosyl protected tetraene



The first set of conditions for trying the double RCM of **4.24** involved use of 20% Grubbs I in CH_2Cl_2 under reflux (Table 4.3, Entry 1). After 72 h, the tricycle **4.25** was obtained in 55% yield with recovered **4.24**, but no **4.26** was observed. We next tried to drive the reaction to completion under microwave heating (Entry 2), but **4.25** was obtained in 60% yield with no detectable amount of the tetracycle. Fearing that the catalyst was decomposing under the reaction conditions, we next tried using stoichiometric amounts of catalyst (Entry 3). The tricycle was the only product obtained from the reaction in 75% yield. We were also worried about any potential isomerization of the olefin that could happen with the ruthenium catalyst after prolonged reaction times. Catalytic amounts of benzoquinone (BQ) are reported to prevent the isomerization.[270] In the event, heating **4.24** with Grubbs I and BQ in the microwave only resulted in the tricyclic compound (Entry 4). The tetracycle was not observed by LC-MS or ^{1}H NMR

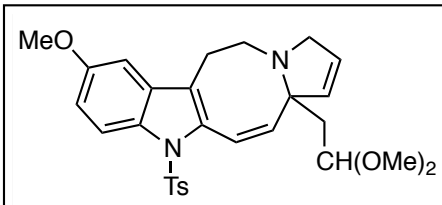
spectroscopy. Portion-wise addition of Grubbs I catalyst (Entry 5) also failed to generate the tetracycle, as did a switch to Grubbs II in $PhCH_3$ (Entry 6). When the reaction was performed in C_7F_8, the LC-MS of the unpurified reaction mixture indicated the maximum theoretical yield of the tricycle that could be obtained was in the 80% range (Entries 7 and 8). Unfortunately, none of the desired tetracycle was observed in this reaction. Again, we performed numerous other reactions with the tosyl-protected tetraene **4.24** by exposing to various ruthenium catalysts and reaction conditions. Unfortunately, in most cases the only isolable compound was the tricycle; the tetracycle **4.26** still remained elusive.

Table 4.3 Attempted double RCM of *N*-tosyl protected tetraene



4.24 **4.25**

Entry	Catalyst	Loading (%)	Conditions	Solvent	Yield of **4.25** (%)
1	Grubbs I	20	Δ, 72 h	CH_2Cl_2	55
2	Grubbs I	20	μW, 55 ˚C	CH_2Cl_2	60
3	Grubbs I	100	μW, 55 ˚C, 12 h	CH_2Cl_2	75
4	Grubbs I	10% x 2	BQ, μW, 55 ˚C, 12 h	CH_2Cl_2	--
5	Grubbs I	10% x 2	μW, 55 ˚C	PhH	--
6	Grubbs II	10	rt	$PhCH_3$	--
7	G-H II	10% x 3	rt	C_7F_8	86 (LC-MS)
8	G-H II	20	μW, 100 ˚C	C_7F_8	82 (LC-MS)



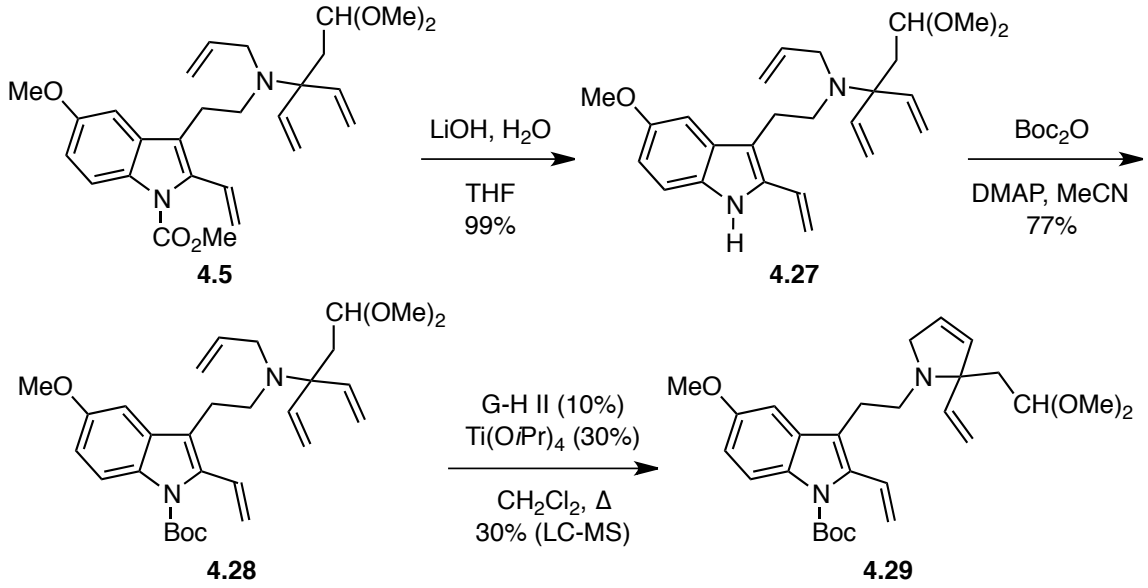
4.26
not observed

4.1.4 Boc-protected double RCM precursor

An *N*-Boc-protected indole tetraene was also explored as a double RCM candidate (Scheme 4.5). The nitrogen atom of the indole **4.5** was deprotected to give the *N*-H compound **4.27** in 99% yield. The Boc protected indole **4.28** was obtained in 77% yield by treating **4.27** with Boc anhydride in the presence of a stoichiometric amount of DMAP. Upon exposure of tetraene **4.28** to Grubbs-Hoveyda II and catalytic $Ti(O\textit{i}Pr)_4$ in CH_2Cl_2, the tricycle **4.29** was obtained in 30% yield. The remaining mass balance for the reaction was recovered starting material; none of the desired tetracycle was detected in

the reaction. At this time we were faced a significant challenge with the double RCM in the indole system. None of the conditions led to even a trace of the desired product, and we were beginning to doubt whether the double RCM was possible with the current approach. Concurrent with our efforts in exploring the double RCM of the indole tetraene, we were also investigating a non-indole route to the lundurine core.

Scheme 4.5 Unproductive double RCM attempt with Boc-protected tetraene

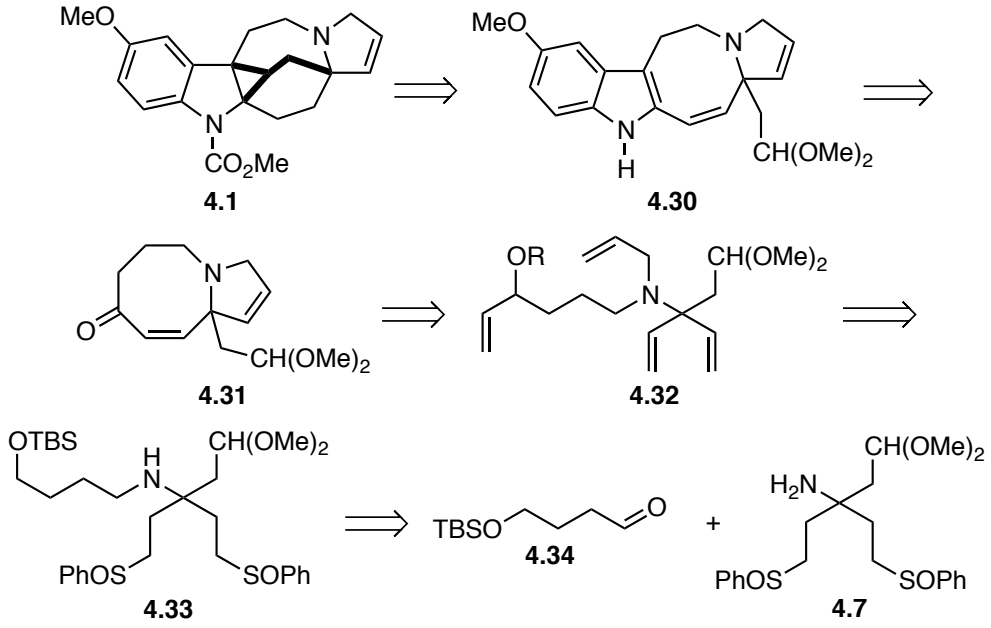


4.2 Development of an Acyclic Double RCM Precursor

We queried whether the indole ring was preventing metathesis through steric interactions with the C(2) vinyl group and sought a way to access a double RCM substrate that did not contain an indole ring system. The natural product **4.1** would arise from the *N*-H indole tetracycle **4.30** after a series of steps including *N*-protection as the methylcarbamate, acid catalyzed hydrolysis of the acetal, hydrazone formation of the aldehyde, [3+2] dipolar cycloaddition to form the pyrazoline, and thermal- or photo-induced dinitrogen extrusion (Scheme 4.6). Tetracycle **4.30** would arise from a late-

stage Fischer indole synthesis of octenone **4.31**. The enone **4.31** would arise from the double RCM product of **4.32** after deprotection and oxidation of **4.32**. The tetraene **4.32** would be obtained upon *N*-allylation and sulfoxide elimination of **4.33**. Bisphenylsulfoxide **4.33** would be obtained from the reductive amination of commercially available aldehyde **4.34** and the acetal containing amine **4.7**.

Scheme 4.6 Retrosynthesis of an acyclic tetraene

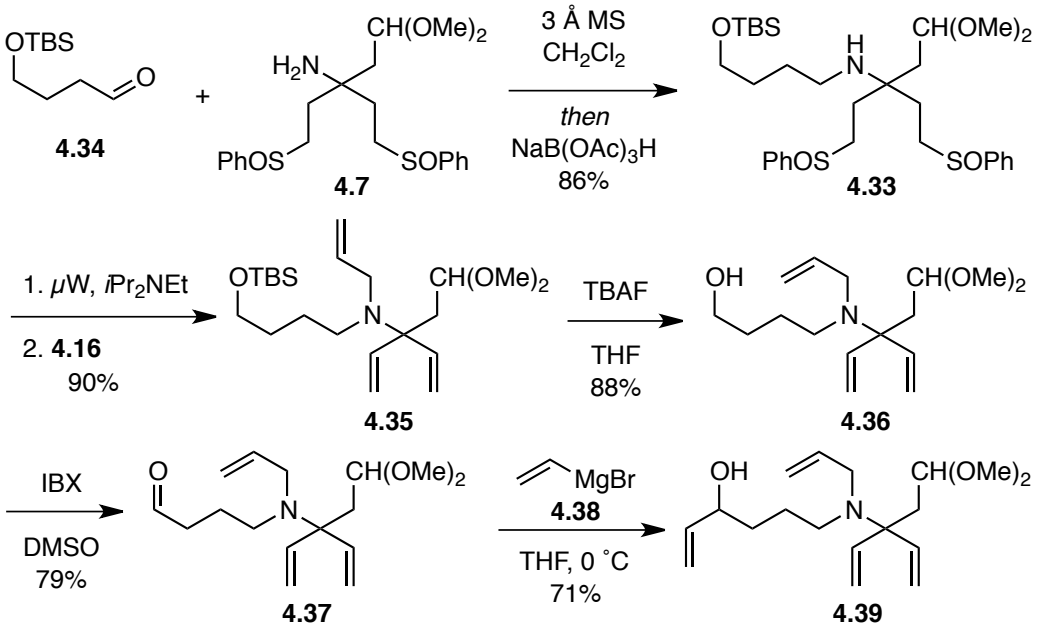


4.2.1 Synthesis of the acyclic tetraene

The preparation of acyclic tetraene **4.32** began with the reductive amination of the imine formed by condensation of aldehyde **4.34** and amine **4.7** (Scheme 4.7). The secondary amine **4.33** was isolated in 86% yield as an inconsequential mixture of diastereomers. Heating **4.33** with excess *i*Pr_2NEt in the microwave oven at 150 ˚C provided a 93% yield of the divinyl compound **4.34**, which was then allylated with **4.16** in a sealed tube to furnish the triene **4.35** in 97% yield. Removal of the TBS group was accomplished using TBAF to deliver the primary alcohol **4.36** in 88% yield. The alcohol

group was subsequently oxidized to the aldehyde **4.37** with IBX in DMSO in 79% yield. The aldehyde **4.37** was then treated with vinyl magnesium bromide to give the desired tetraene **4.38** in an unoptimized 71% yield. With tetraene **4.38** in hand, the double RCM of the acyclic tetraene was next investigated.

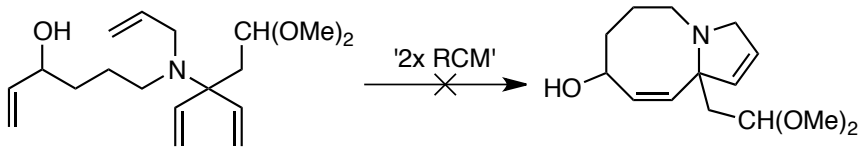
Scheme 4.7 Synthesis of the acyclic tetraene



With limited quantities of tetraene **4.39** in hand, we had to be selective in terms of reaction conditions for the RCM. The initial RCM of **4.39** was attempted with Grubbs I using conventional heating methods (Table 4.4). By LC-MS, a significant amount of starting material was present, but prolonged heating did not push the reaction to completion. Upon analysis of the crude reaction mixture, no mass consistent with the desired product **4.40** was observed in the LC-MS; however, masses consistent of a monocycle **4.41**, **4.42** or **4.43** were present. The identity of the monocycle that was formed in the reaction was unknown, but the current study could still lead to positive results so additional conditions were screened. More forcing conditions were explored

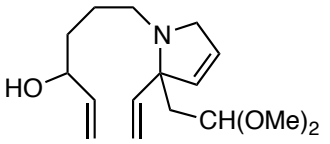
with the hopes of pushing the reaction to completion (Entry 2). Starting material was still recovered after the reaction, and a mass consistent with a monocycle was seen after analyzing LC-MS data. Believing the basic amine was preventing cyclization from occurring, **4.39** was treated with anhydrous *p*-TsOH and Grubbs II with hopes that the tosylate salt would then undergo the RCM. Unfortunately, there was immediate decomposition upon heating, and nothing useful was obtained after purification. There was enough material for one more attempt (Entry 4). Upon exposure of **4.39** to Grubbs I and catalytic $Ti(O\textit{i}Pr)_4$ in the microwave oven, numerous products were formed. After purification of the reaction mixture, methyl ketone **4.44** was isolated in 20% yield, the structure of which was elucidated by ^1H NMR spectroscopy.

Table 4.4 Attempted double RCM of the linear tetraene

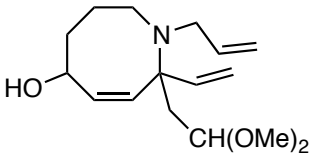


4.39 **4.40**

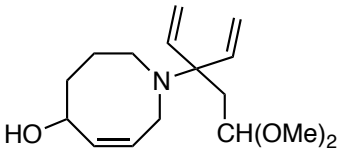
Entry	Catalyst	Loading (%)	Conditions	Solvent	Result
1	Grubbs I	10% x 2	Δ	CH_2Cl_2	Monocycle + RSM
2	Grubbs II	10	100 ˚C	$PhCH_3$	Monocycle + RSM
3	Grubbs II	10	100 ˚C	$PhCH_3$	Dec.
4	Grubbs I	20% x 2	$Ti(OiPr)_4$, μW	CH_2Cl_2	**4.44** (20% isolated)



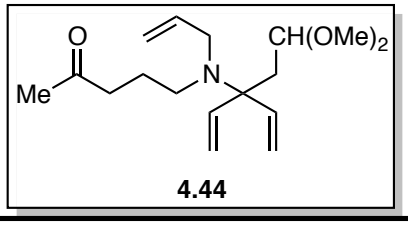
4.41



4.42



4.43

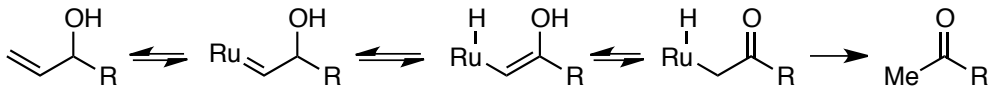


4.44

The ruthenium catalyzed formation of methyl ketones from allylic alcohols has been reported on numerous occasions, and a mechanism for the reaction has been proposed by Hoye and coworkers (Figure 4.1).[271] Upon catalyst loading onto the olefin of the allylic alcohol **4.45**, the carbene **4.46** undergoes tautomerization to the enoyl ruthenium hydride **4.47**, which then tautomerizes to the ketone **4.48**. Subsequent reductive elimination of **4.48** delivers the methyl ketone **4.49**. After this result was obtained, the previous reactions in Table 4.4 were inspected in detail, and the LC-MS chromatograms as well as the ^{1}H NMR spectra indicated the presence of the methyl ketone side product.

Hoye proposed two solutions to this problem: the use of stoichiometric amounts of Grubbs catalyst or protection of the alcohol. Considering the synthetic cost of tetraene **4.39** and the financial cost of the metathesis catalyst, the latter option was chosen.

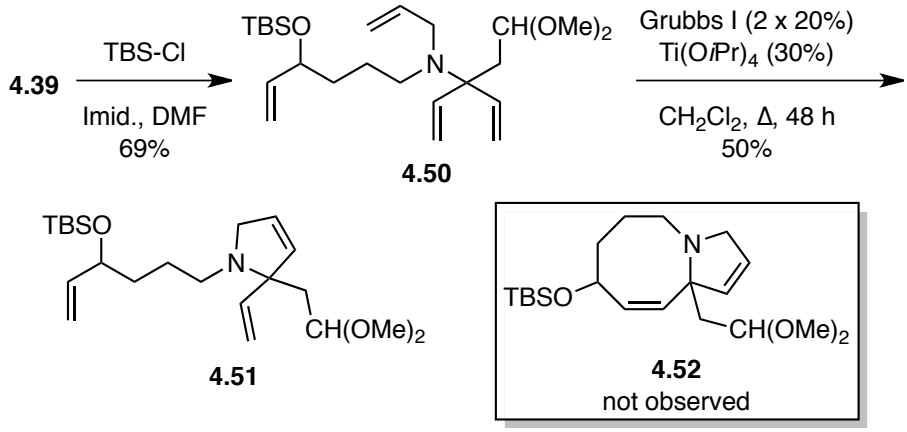
Figure 4.1 Proposed mechanism of methyl ketone formation



4.45 **4.46** **4.47** **4.48** **4.49**

The TBS protection of alcohol **4.39** occurred without incident and **4.50** was obtained in 69% yield (Scheme 4.8). When **4.50** was exposed to two 20% portions of Grubbs II catalyst with a titanium additive for 48 h, the monocycle **4.51** was isolated in 50% yield as the only product. Gratifyingly, no methyl ketone side product **4.44** was observed, but neither was there any indication that the second ring had formed to give the bicyclic compound **4.52**. Although the reaction failed to give the desired product, the results did direct us to explore the amine acetal substrate. The data suggested that the ruthenium catalyst loaded onto the allylic amine olefin rather than the allylic alcohol olefin. The next course of action was to deactivate the allyl amine moiety altogether by making the crotonamide derivative. Protonation was also possible; however, we decided not to pursue this option since the previous attempts of performing an RCM on protonated material were unsuccessful.

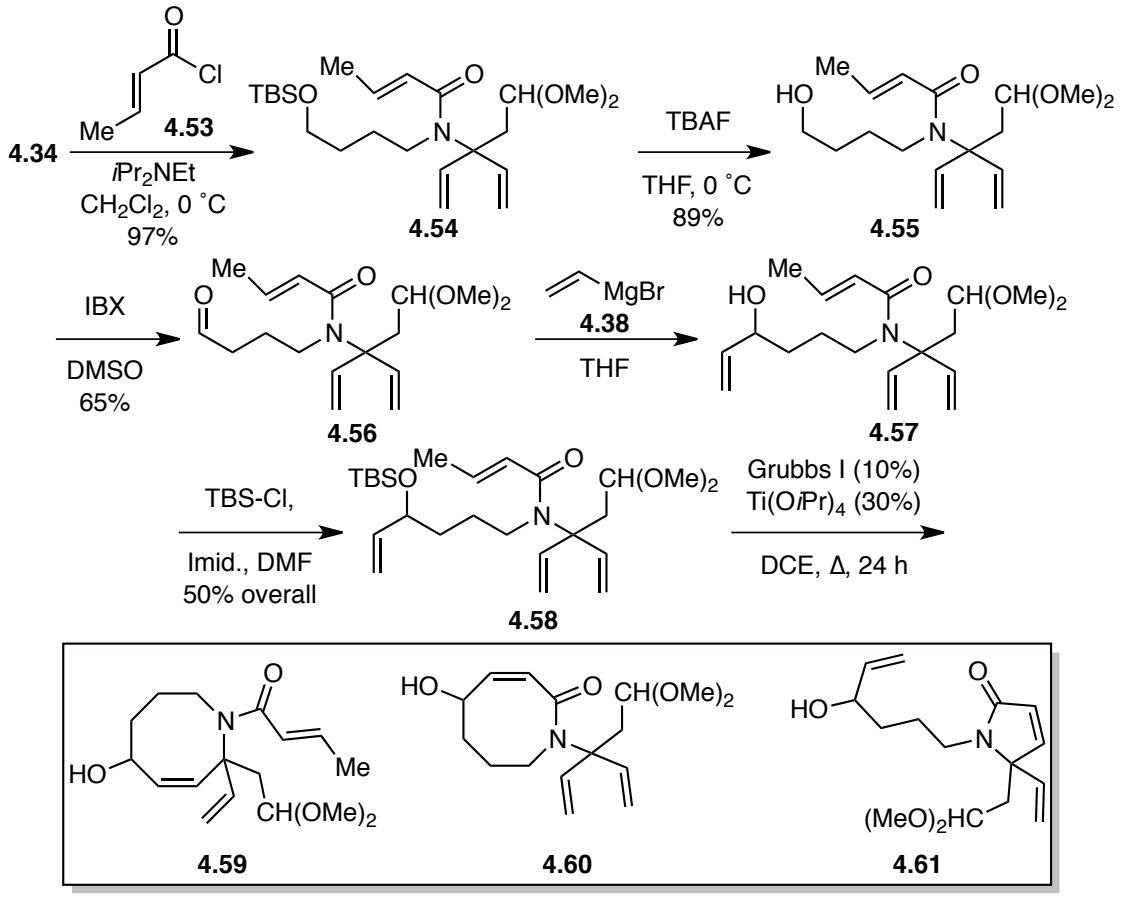
Scheme 4.8 Attempted double RCM of acyclic tetraene with protected alcohol



4.2.2 Preparation of a crotonamide acyclic tetraene

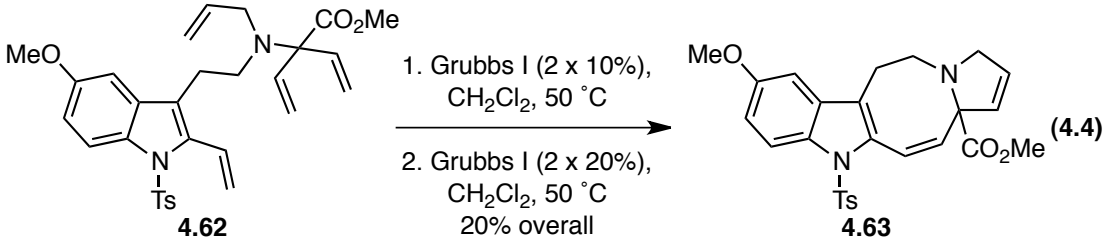
The synthesis of the crotonamide tetraene **4.58** was relatively straightforward and is shown in Scheme 4.9. Secondary amine **4.35** was first treated with crotonoyl chloride (**4.53**), and the amide **4.54** was isolated in 97% yield. The TBS group was removed using TBAF to provide **4.55** in 89% yield, and the alcohol moiety of **4.55** was oxidized with IBX in DMSO to the aldehyde **4.56** in 65% yield. The vinyl group was installed, and the alcohol of **4.57** was protected as its TBS ether to give **4.58** in 50% overall yield. There was sufficient material for one attempt to induce a double RCM. In the event, exposing tetraene **4.58** to Grubbs I in 1,2-dichloroethane under reflux gave a mixture of many products as indicated by LC-MS and TLC analyses. The data indicated that the TBS group on the oxygen did not survive the conditions of the reaction, and masses consistent with the compounds **4.59**, **4.60** and **4.61** were present in the mixture. Frustratingly, the double RCM product was not detected in the unpurified reaction mixture.

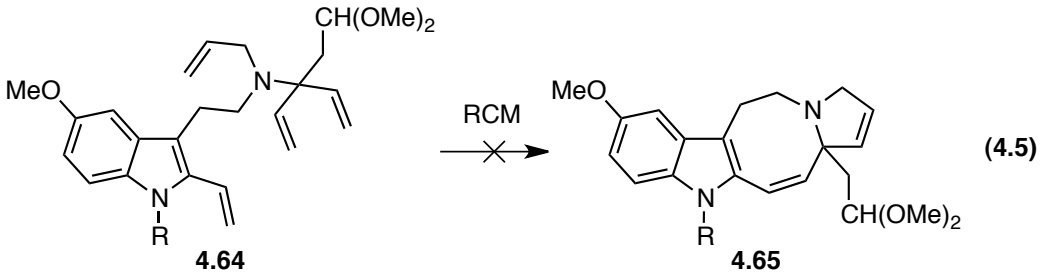
Scheme 4.9 Preparation of the crotonamide tetraene



At this point we realized this approach to lundurine B (**4.1**) with the acetal amine **4.7** was not as simple as had been expected. There was no evidence that the eight membered ring was formed under any conditions, and the metathesis reactions themselves suffered from poor yields, low conversions, and formation of side products. We took a closer at the double RCM reaction in the first generation route that was reported by Dr. Orr and compared it to the tetraene **4.64**. The tetraene **4.62** contains one less methylene unit, and the alcohol is at the ester oxidation state. These relatively subtle differences in structure apparently allow the double RCM to proceed to give a compound that was tentatively assigned to be tetracycle **4.63** (Equation 4.4). Tetraene **4.64** contains

an additional methylene and an acetal. Under a variety of RCM conditions, there was no evidence that **4.65** was formed (Equation 4.5). One option available to us was to eliminate the acetal altogether and use a protected primary alcohol instead. We reasoned that this could minimize the steric environment around the already crowded vinyl olefins, which could in turn give the metathesis catalyst easier access to the remaining olefin to form the eight membered ring after the first ring closure. We decided to pursue this route and incorporate a primary protected alcohol instead of the bulkier acetal.



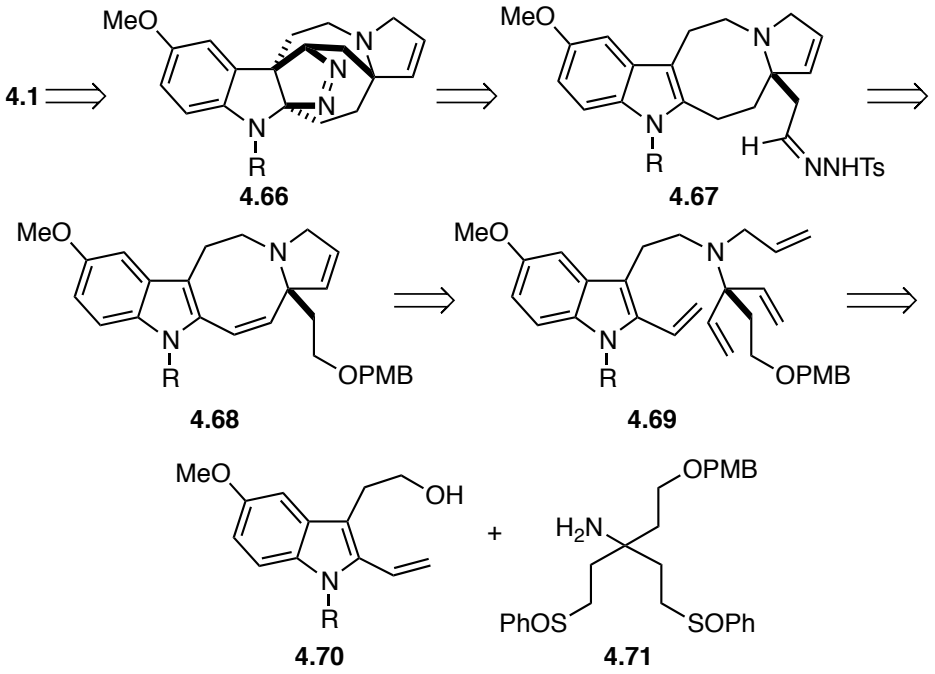


4.3 Approach to Lundurine B Using a Protected Primary Alcohol

This new entry is outlined in retrosynthetic form in Scheme 4.10. We chose to protect the primary alcohol as the PMB protecting group because of the numerous conditions known for its removal. The endgame from **4.66** to lundurine B (**4.1**) is identical to that proposed in Scheme 4.1. The tetracycle **4.68** would arise from **4.69** after hydrogenation of the eight membered ring, PMB removal, oxidation of the resulting alcohol to the aldehyde, and then hydrazone formation. We were still set on incorporating a double RCM as a key step in the synthesis to convert tetraene **4.69** to

tetracycle **4.68** after sulfoxide elimination and allylation of the amine. Finally, **4.69** would be obtained after reductive amination of indole **4.70** and amine **4.71**.

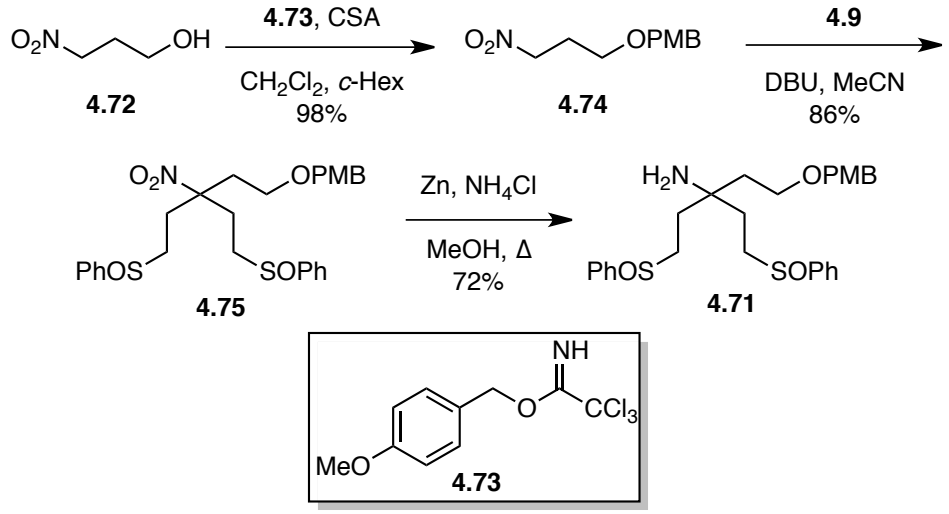
Scheme 4.10 Retrosynthesis to lundurine B featuring a PMB-protected alcohol



4.3.1 Synthesis of the non-acetal amine

The route presented in Scheme 4.10 required the preparation of the amine **4.71**. Beginning with 3-nitropropanol (**4.72**), available in two steps from acrolein, alcohol protection with PMB trifluoroacetimidate (**4.73**) with camphorsulfonic acid (CSA) as catalyst provided **4.74** in 98% yield (Scheme 4.11).[263] Treatment of **4.74** with **4.9** provided **4.75** in 86% yield, and reduction of **4.75** using the Zn and NH_4Cl conditions that worked with the acetal amine delivered the amine **4.71** in 72% yield.

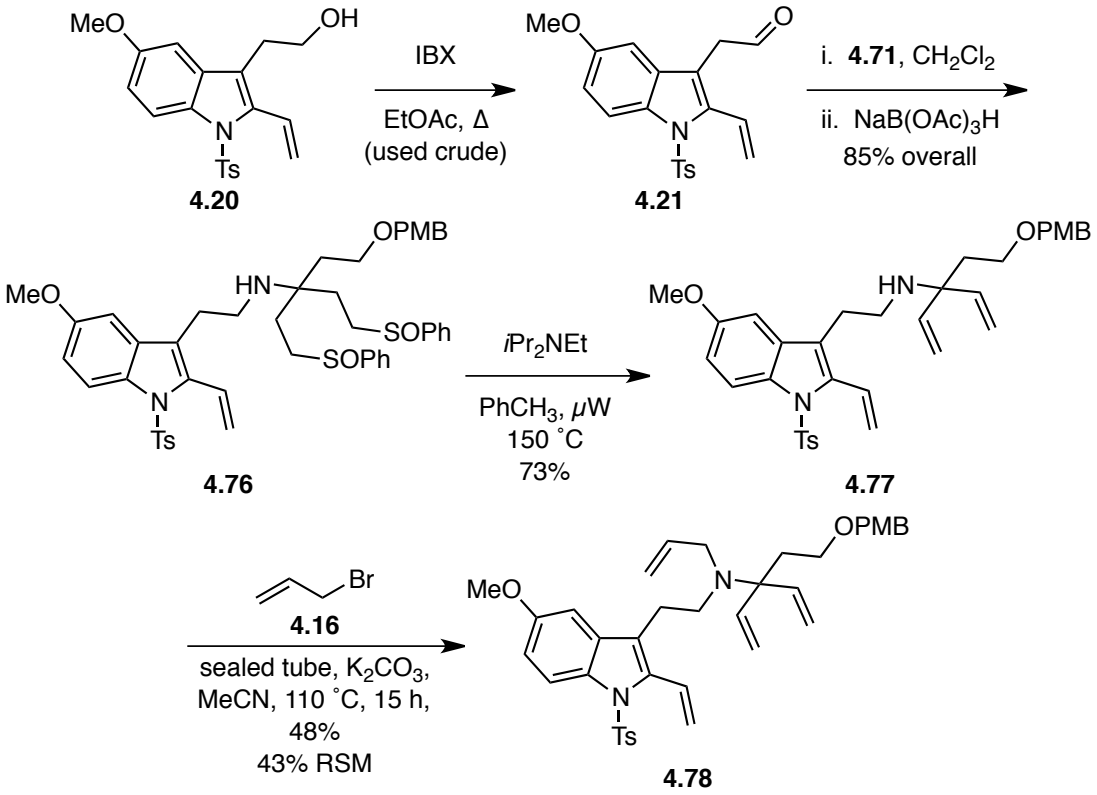
Scheme 4.11 Preparation of the amine with PMB-protected alcohol



4.3.2 Synthesis of the *N*-tosyl protected tetraene

The *N*-tosyl protected indole **4.20** was used rather than the *N*-methylcarbamate protected indole alcohol **4.6** because we wanted to have an indole tetraene that closely mimicked the first generation tetraene **4.62**. Alcohol **4.20** was oxidized to the aldehyde, which then underwent reductive amination with amine **4.71** to provide **4.76** in 85% yield. The phenyl sulfoxide groups of **4.76** were eliminated upon microwave heating at 150 ˚C in the presence of *i*Pr_2NEt to give **4.77** in 73% yield, and *N*-allylation delivered the tetraene **4.78** in an unoptimized 48% yield. With **4.78** in hand, we turned our attention to the double RCM.

Scheme 4.12 New route to the *N*-tosyl protected tetraene **4.78**

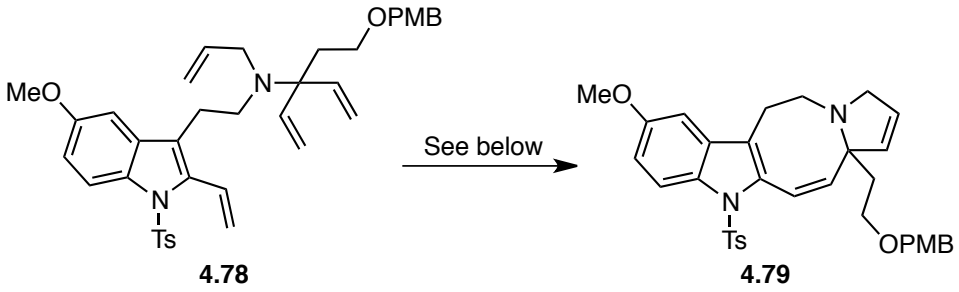


Our first attempts to induce the RCM of **4.78** involved use of Grubbs I catalyst and microwave heating at 50 °C (Table 4.5, Entry 1). The main products were the tricycle **4.80** and recovered starting amine **4.79**. A compound having a mass consistent with that of the tetracycle **4.79** was not seen by LC-MS. We then attempted to drive the reaction to completion by using more forceful conditions, whereupon we isolated a compound having a mass and ^{1}H NMR spectrum that appeared to be consistent with tetracycle **4.79** in ~20% yield. We queried whether the less reactive Grubbs I could perform the double RCM (Entry 3). Unfortunately, a mixture of the proposed tetracycle **4.79** and an unknown side product was obtained.

At this point we queried whether the *N*-methyl carbamate tetraene with the PMB-protected alcohol might undergo the double RCM. Lundurine B (**4.1**) contains an *N*-

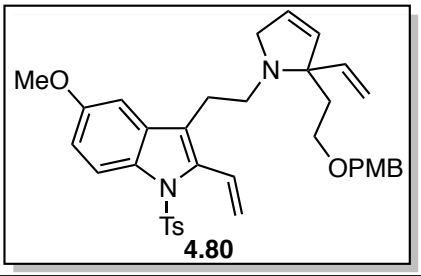
methylcarbamate protected indole nitrogen atom, thus a number of steps would be saved if the double RCM was successful with the *N*-methylcarbamate installed from the beginning.

Table 4.5 Synthesis of the tentatively assigned tetracyclic structure **4.79**



4.78 **4.79**

Entry	Catalyst	Loading (%)	Solvent	Conditions	Result
1	Grubbs I	20	CH_2Cl_2	μW, 50 ˚C, 6 h	46% **4.80** + **4.78**
2	Grubbs II	20% x 2	DCE	μW, 83 ˚C, 9 h	20% **4.79** + SP
3	Grubbs I	40	DCE	μW, 83 ˚C, 12 h	**4.79** and SP



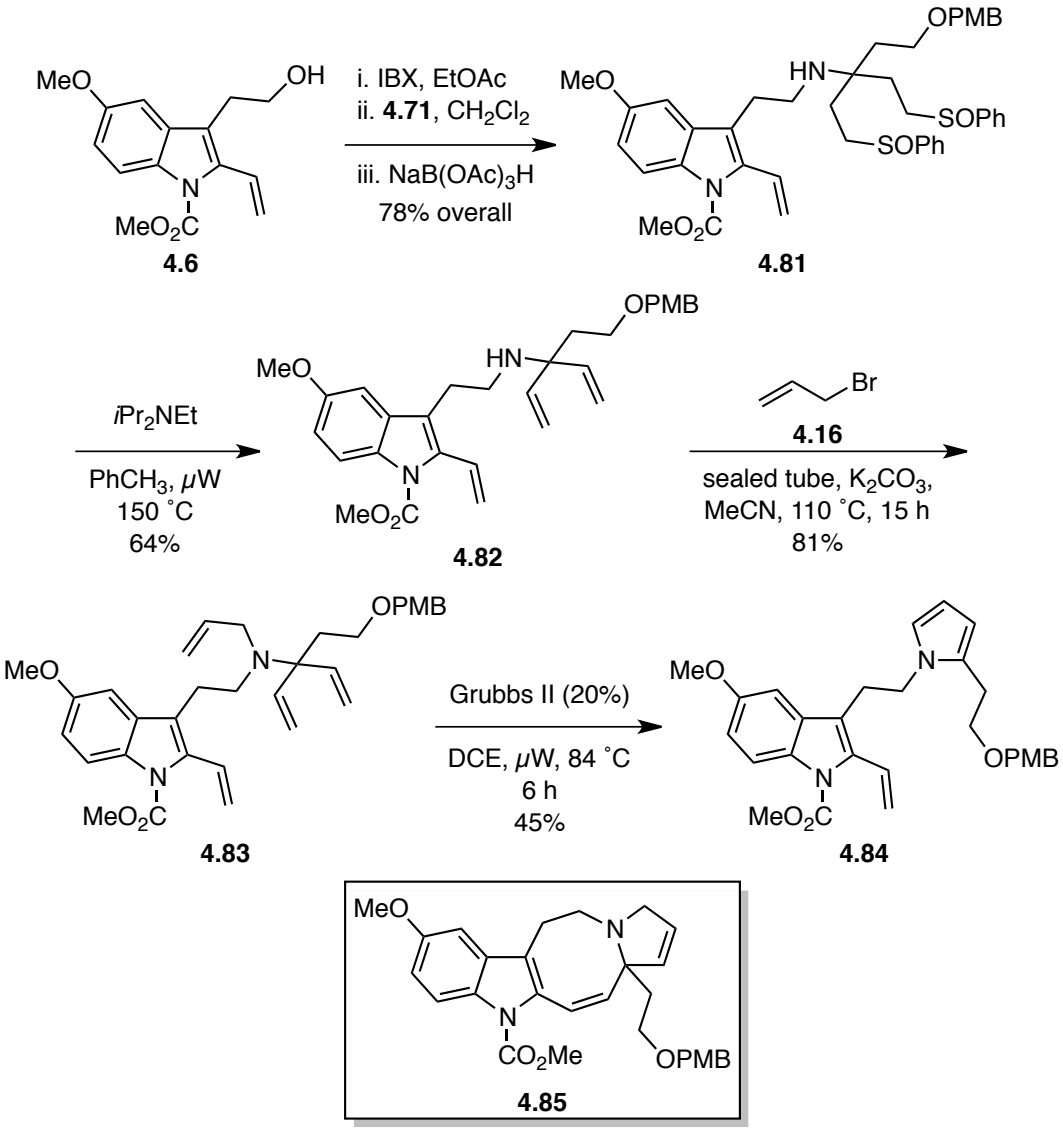
4.80

4.3.3 Synthesis of the *N*-methylcarbamate tetraene and double RCM

The synthesis of the new tetraene commenced with oxidation of **4.6** followed by reductive amination with **4.71** provided the amine **4.81** in 78% yield (Scheme 4.13). Elimination of the sulfoxides occurred under standard conditions to deliver **4.82** in 64% yield, and allylation of the nitrogen atom of **4.82** took place in 81% yield to furnish tetraene **4.83**. Surprisingly, the attempted double RCM of **4.83** in the microwave oven with the second-generation Grubbs catalyst provided the pyrrole **4.84** in 45% yield; the

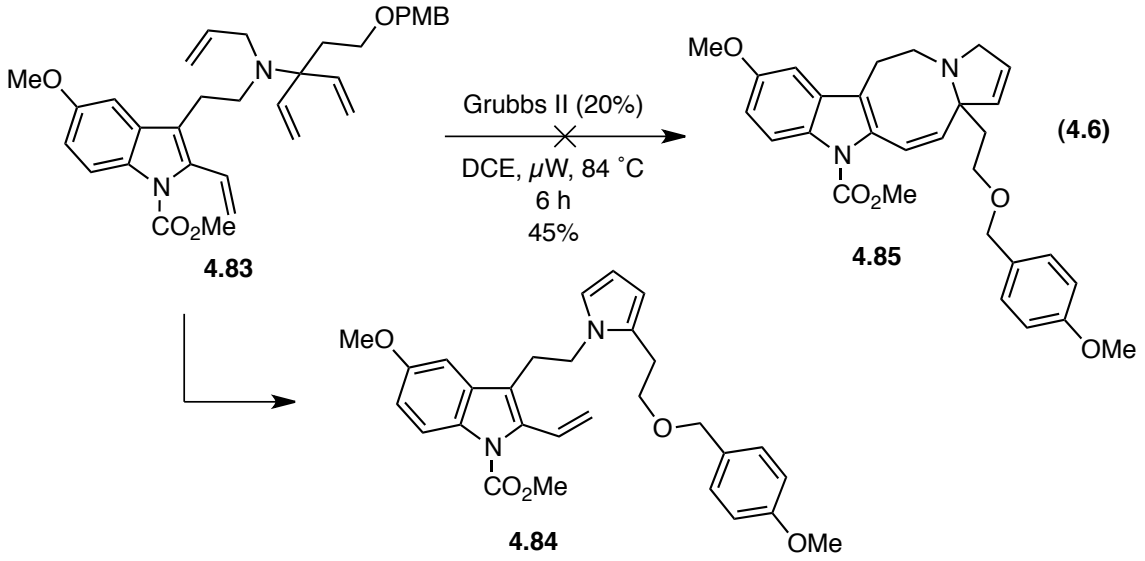
desired tetracycle **4.85** was not detected in the crude reaction mixture. Attempts to lower the catalyst loading, use other ruthenium RCM catalysts, shorten reaction time, and increase the scale of the reaction using conventional heating methods gave lower yields of the pyrrole product **4.84** and none of the desired tetracycle **4.85**. The structure of **4.84** was supported by NMR techniques (*vide infra*). The chemical formula of pyrrole **4.84** and tetracycle **4.85** are identical, making it impossible to distinguish the two compounds by mass spectroscopy.

Scheme 4.13 Preparation of the tetraene and formation of pyrrole **4.84**



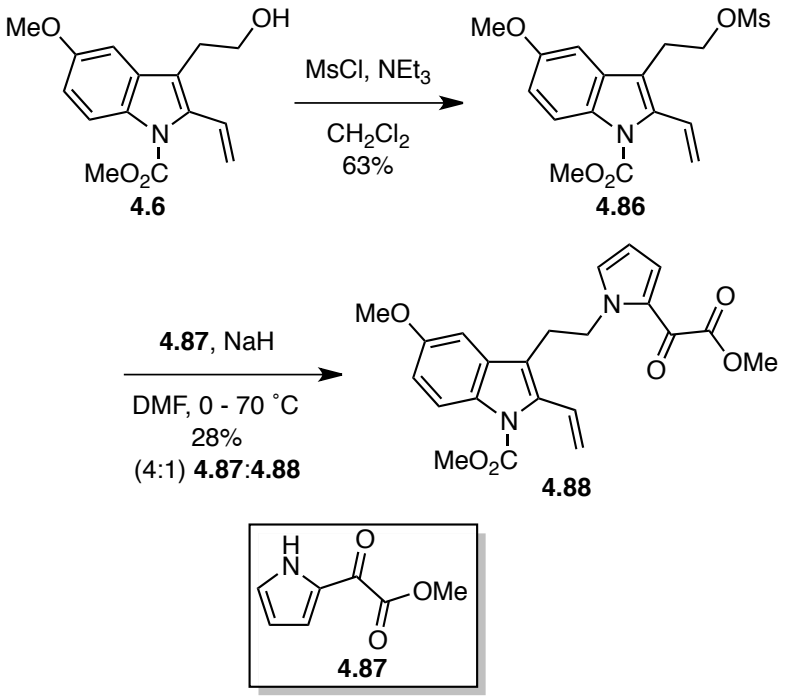
There were several indicative features in the NMR spectral data that suggested that the pyrrole **4.84** was obtained instead of the desired tetracycle **4.85** (Equation 4.6). For example, a vinyl group is present at the C(2) position of the indole. The position of the C(2) vinyl group of **4.84** was similar to the position of the C(2) vinyl group of the starting tetraene **4.83**. Evidence to support its presence includes the correct splitting patterns for the vinyl protons, the expected coupling constants and chemical shifts for a

vinyl group at δ 6.87, 5.25, and 4.97 ppm in C_6D_6, and the correct ^1H-^1H cross-peaks in the COSY 2D NMR. Further evidence comes from the ^{13}C NMR data. The pyrrole **4.84** contains eight sp^3 hybridized carbon atoms, whereas the tetracycle **4.85** contains nine sp^3 hybridized carbon atoms. The ^{13}C NMR spectrum of **4.84** showed eight resonances within the aliphatic region with no overlapping signals.

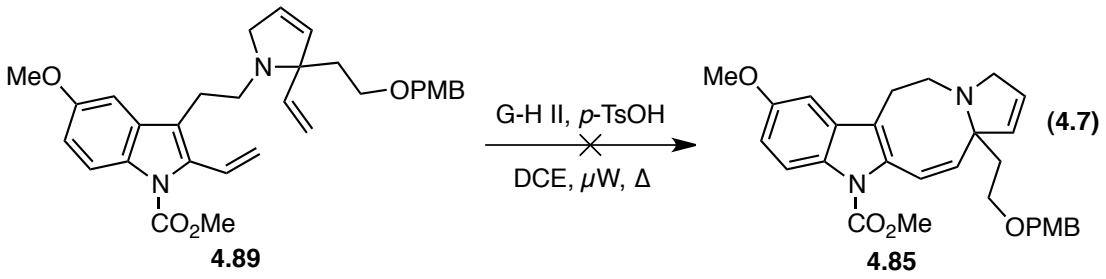


A preliminary attempt to prepare **4.84** in an independent synthesis has so far been unsuccessful. Thus, alcohol moiety of indole **4.6** was activated as its mesylate derivative **4.86** in 63% yield; however, displacement of the mesylate with the anion of **4.87** provided an inseparable mixture (4:1) of **4.87** and the alkylated product **4.88**.

Scheme 4.14 Attempted independent preparation of pyrrole **4.84**

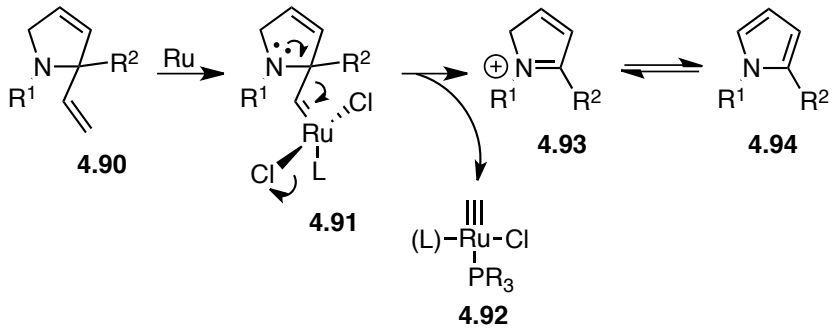


The formation of the pyrrole side product **4.84** is puzzling because such a fragmentation during an RCM has not been reported in the literature. We queried whether protonation of the nitrogen atom would prevent the fragmentation by tying up the reactive lone pair, but exposure of monocylized product **4.89** to Grubbs-Hoveyda II in the presence of anhydrous TsOH afforded none of the tetracycle **4.85** (Equation 4.7). An intractable mixture of products was obtained instead, and the pyrrole **4.84** was not detected in the crude reaction mixture. The second generation Grubbs-Hoveyda catalyst was used in this experiment because its use gave more consistent results although somewhat lower yields of the pyrrole product **4.84** relative to Grubbs II during catalyst screening.



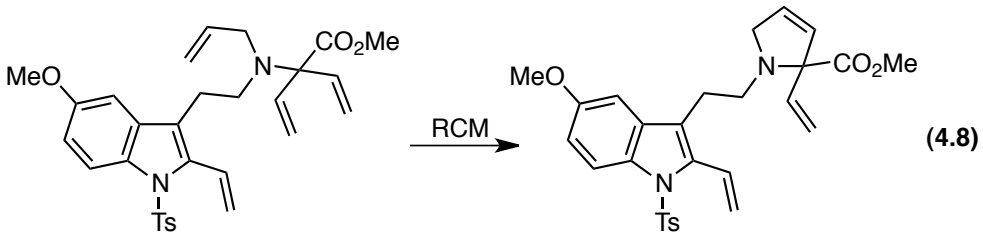
The mechanism by which the pyrrole **4.84** is unknown because the reaction is unprecedented. The pyrrole **4.84** was only formed when the second-generation Grubbs and Hoveyda-Grubbs catalysts were used, which may be of importance for future studies of the reaction. At the moment, the best proposal for the fragmentation is shown in Scheme 4.15. The ruthenium catalyst presumably loads onto the vinyl olefin of the monocyclized product **4.90** to form intermediate **4.91**. The nitrogen lone pair could facilitate the fragmentation of **4.91** and displacement of the organometallic complex **4.92** with formation of the iminium ion **4.93**, which would tautomerize to the pyrrole **4.94**. No studies have been performed on the mechanism proposed in Scheme 4.15. The study of ruthenium acetylenes has been studied computationally,[272] but experimental investigations have not been reported.

Scheme 4.15 Proposed mechanism of pyrrole formation



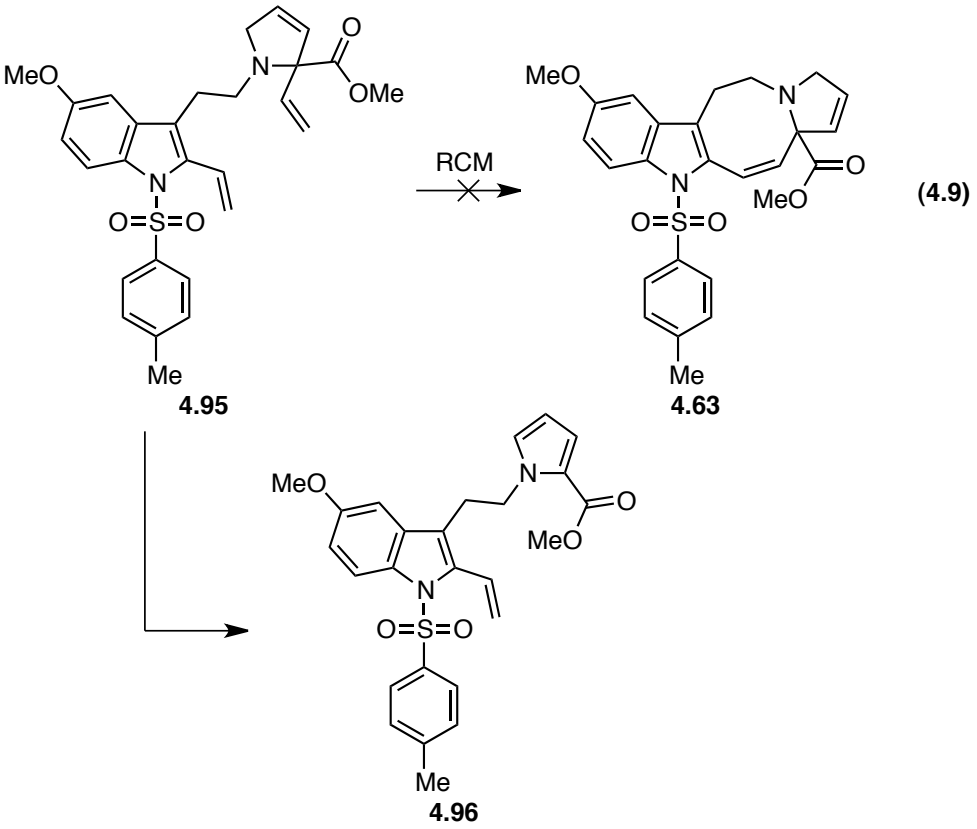
4.4 POTENTIAL STRUCTURAL MISASSIGNMENT

We were surprised with the result of the attempted double RCM with the tetraene **4.83** and wondered whether the same pyrrole side product might have been formed in the double RCM reported by Dr. Orr. We first closely examined all spectral data associated with the tetraene **4.62** as well as the monocyclized product **4.95** (Equation 4.8), and after extensive inspection concluded that the structural assignments of **4.62** and **4.95** were correct.



4.62 **4.95** **(4.8)**

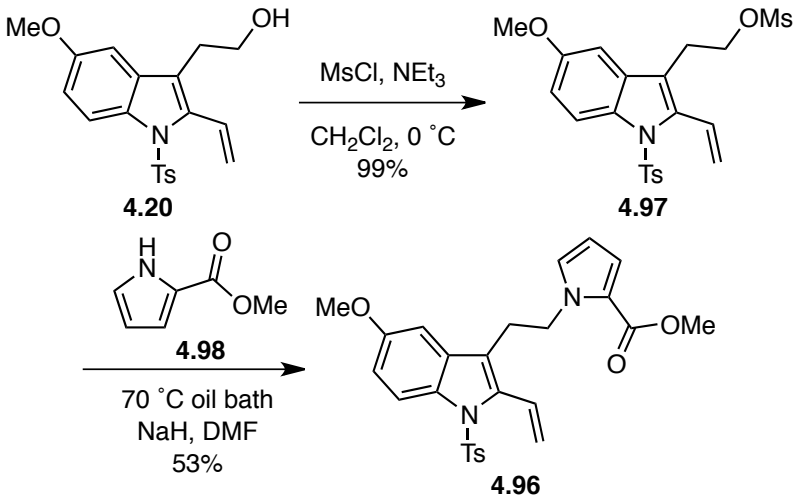
We then queried whether the structural assignment of **4.63** was correct. Upon careful examination we noted that there were a number of peaks in the ^{1}H NMR spectrum of this compound that could not originate from **4.63**. Because the ^{13}C NMR spectrum had a very high signal to noise ratio, interpretation of the 2D NMR spectral data obtained for the small amounts of **4.63** was difficult to interpret. This made assignments of each proton and carbon atom by a 2D HSQC NMR experiment in the presumed tetracyclic compound **4.63** unreliable. However, after analyzing the 1D and 2D NMR data of the Orr product in detail, we surmised that the assigned structure was likely incorrect (Equation 4.9). We believed that what had been assigned as the tetracycle **4.63** was actually the tricyclic pyrrole **4.96**. In order to unequivocally prove our hypothesis, we prepared the pyrrole **4.96** by an independent route. If the spectral data of synthetic **4.96** matched the data reported for **4.63**, we would have indisputable evidence that the structure of **4.63** was in fact misassigned.



The alternative synthesis of **4.96** began with the activation of the alcohol moiety of **4.20** to the mesylate **4.97** in 99% yield (Scheme 4.16). Upon stirring a mixture of **4.97** with 2-carbomethoxypyrrole (**4.98**) in DMF with NaH as base, the alkylated product **4.96** was obtained in 53% yield. The ^{1}H, ^{13}C, HSQC, HMBC, and COSY NMR spectral data of the synthetic pyrrole **4.96** matched that of the material Orr isolated from the attempted double RCM reaction of **4.62**. The ^{1}H, ^{13}C and 2D NMR data for **4.96** were recorded on significantly cleaner and larger amounts of material, which made assignment of each carbon and hydrogen atom simpler. One of the indicative features that **4.96** was actually obtained from the double RCM rather than **4.63** was the presence of a vinyl group on the C(2) indole position. The three unique splitting patterns and coupling constants within the ^{1}H NMR spectrum for protons at δ 7.19, 5.27, and 5.00 in addition to the expected COSY cross peaks within the 2D NMR were consistent with those of a vinyl group. The

2D ^{1}H-^{13}C NMR HSQC correlation experiment provided even further evidence that a vinyl group was present. A ^{13}C DEPT experiment verified the correct number of methyl, methylene, and methine carbon atoms that would be expected in pyrrole **4.96**. Additionally, the tetracycle **4.63** contains six sp^3 carbon atoms while **4.96** has only five. In the ^{13}C NMR spectrum of **4.96**, there are only five peaks in the aliphatic region, not six as expected for **4.63**. Using a combination of the HSQC, HMBC, DEPT and COSY, each carbon and hydrogen atom was assigned, which verified the structure of **4.96**. From these experiments, we can confidently say that the tetracycle **4.63** was never synthesized.

Scheme 4.16 Independent synthesis of pyrrole **4.96**



4.5 SUMMARY AND CONCLUSIONS

In summary, the attempted synthesis of lundurine B (**4.1**) was unsuccessful. We were able to prepare indole-containing tetraenes with different protecting groups on the indole nitrogen atom with a methyl acetal. Upon attempted double RCM, we obtained a significant amount of the mono-cyclized product. We then prepared a tetraene in which the indole ring was not attached (Scheme 4.7). Again, the double RCM did not provide the desired bicyclic product. Querying whether the acetal was inhibiting the metathesis

for steric reasons, we switched to a PMB-protected primary alcohol (Scheme 4.10). The double RCM of this tetraene at first led us to believe we had obtained the tetracycle. Using this material in the final reactions of the proposed synthesis did not provide us **4.1**. Instead, we learned of a misassignment of a compound that was assumed to be the tetracycle in the first generation synthesis. We then proposed a structure of a pyrrole-containing compound **4.96** that was actually isolated from the reaction, which we then prepared in an independent synthesis (Scheme 4.15). After closely inspecting the NMR spectral data of **4.96**, we realized that it had identical characterization data to that of the presumed tetracycle **4.63**. Thus, a tetracycle was never synthesized using a double RCM.

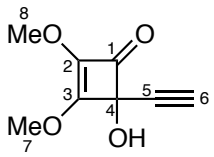
Chapter 5: Experimental Methods

5.1 General Experimental Procedures

Solvents were purified as described by Grubbs.[273] CH_2Cl_2, PhH, and DME were freshly distilled from CaH_2. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon or nitrogen in glassware that had been flame or oven dried overnight. The Jones reagent was prepared as follows: a mixture of CrO_3 (6.68 g, 66.8 mmol) and concentrated H_2SO_4 (5.8 mL) was diluted to 25 mL with H_2O at room temperature to an approximate concentration of 2.67 M. Unless otherwise indicated, commercial materials were used without further purification. Melting points were obtained using a Thomas Hoover Unimelt capillary apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates (0.25 mm, 60 F_{254} indicator) and was visualized using *p*-anisaldehyde, $KMnO_4$, and/or UV light (254 nm).

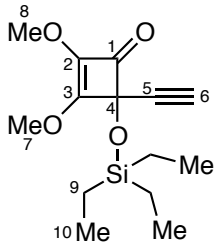
Infrared (IR) spectra were obtained using a Nicolet IR100 FT-IR spectrometer in CH_2Cl_2 solution on sodium chloride plates, and are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance spectra were recorded at the indicated field strength. ^1H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm). Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. Coupling constants (*J*) are reported in Hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons.

5.2 EXPERIMENTAL PROCEDURES



4-Ethynyl-4-hydroxy-2,3-dimethoxycyclobut-2-eneone (2.11). ALN-2-23. MeOH (15 mL) was slowly added to calcium carbide (42 g, 0.66 mol) until acetylene was evolved. H_2O (100 mL) was added over the course of the reaction at a rate to maintain acetylene evolution. The liberated gas was passed through $CaCl_2$ before bubbling into a solution of THF (200 mL) precooled to -78 ˚C. After evolution of acetylene ceased, a solution of *n*-BuLi (45 mL, 1.95 M in Hexanes) in THF (100 mL) at -78 ˚C was transferred to the solution of acetylene using a cannula. The clear solution immediately turned yellow, and the reaction was stirred at -78 ˚C for 30 min. A solution of **2.9** (6.2 g, 0.044 mol) in THF (100 mL) was rapidly added to the lithium acetylide solution using a pressure equalizing jacketed addition funnel at -78 ˚C. The reaction was stirred at -78 ˚C for 1 h, whereupon saturated aqueous NH_4Cl (100 mL) was added. The cooling bath was removed, and stirring was continued for 20 min. The reaction was extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by filtering through a plug of silica (125 g) eluting with Hexanes:EtOAc (3:1). The solid, formed upon standing, was recrystallized from Hexanes/Et_2O to provide 6.09 g (82%) of **2.11** as colorless crystals that must be stored in a freezer under nitrogen: mp 75-76 ˚C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.21 (s, 3 H), 3.98 (s, 3 H), 3.06 (s, 1 H), 2.83 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.5, 166.7, 135.1, 80.5, 79.7, 78.3, 60.6, 59.0; IR (CH_2Cl_2) 3286, 2113, 1779, 1631, 1345 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_8H_9O_4]^+$ (M+H), 169.0423; found, 169.0502.

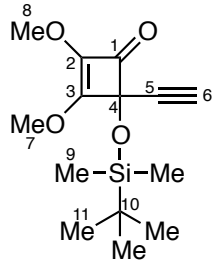
NMR Assignments. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.21 (s, 3 H, C7-H), 3.98 (s, 3 H, C8-H), 3.06 (s, 1 H, C4-OH), 2.83 (s, 1 H, C6-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.5 (C1), 166.7 (C3), 135.1 (C2), 80.5 (C5), 79.7 (C4), 78.3 (C6), 60.6 (C7), 59.0 (C8).



4-Ethynyl-4-[(triethylsilyl)oxy]-2,3-dimethoxy-2-cyclobutene-1-one (2.12). ALN-1-276. NEt_3 (0.23 g, 0.32 mL, 2.3 mmol) was added to a solution of **2.11** (0.30 g, 1.8 mmol) and freshly distilled TES-Cl (0.35 g, 0.39 mL, 2.3 mmol) in THF (20 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 2 h and then at room temperature for 12 h. The reaction was quenched with chilled saturated aqueous NH_4Cl (20 mL), and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15 g silica gel) eluting with Hexanes:EtOAc (3:1) with 1% NEt_3 to give 0.48 g (94%) of **2.12** as a pale yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 4.18 (s, 3 H), 3.96 (s, 3 H), 2.77 (s, 1 H), 0.97 (t, J = 7.2 Hz, 9 H), 0.73 (q, J = 7.2 Hz, 6 H); ^{13}C NMR (100 MHz, C_6D_6) δ 178.5, 164.0, 134.8, 79.2, 79.1, 76.1, 58.3, 57.1, 6.1, 5.0; IR (CH_2Cl_2) 2109, 1782, 731 cm^{-1}; HRMS (ESI) m/z calculated for $[C_{14}H_{22}NaO_4Si]^+$ (M+Na), 305.11851; found, 305.11796.

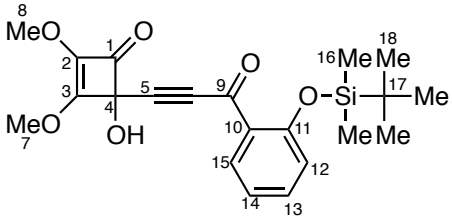
NMR Assignments. ^{1}H NMR (400 MHz, C_6D_6) δ 4.18 (s, 3 H, C7-H), 3.96 (s, 3 H, C8-H), 2.77 (s, 1 H, C6-H), 0.97 (t, J = 7.2 Hz, 9 H, C10-H), 0.73 (q, J = 7.2 Hz, 6 H,

C9-H); ^{13}C NMR (100 MHz, C_6D_6) δ 178.5 (C1), 164.0 (C3), 134.8 (C2), 79.2 (C5), 79.1 (C4), 76.1 (C6), 58.3 (C7), 57.1 (C8), 6.1 (C9), 5.0 (C10).



4-Ethynyl-4-[(*tert*butyldimethylsilyl)oxy]-2,3-dimethoxy-2-cyclobutene-1-one (2.13). ALN-1-227. Imidazole (0.23 g, 3.3 mmol) was added to a solution of **2.11** (0.43 g, 2.6 mmol) and TBS-Cl (1.16 g, 7.7 mmol) in DMF (13 mL) at room temperature. The reaction was stirred for 14 h, chilled H_2O (5 mL) was added, and the product was washed with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15 g silica gel) eluting with Hexanes:EtOAc (3:1) with 1% NEt_3 to afford 0.21 g (29%) of **2.13** as a low melting yellow solid: mp 31-32 °C; ^{1}H NMR (400 MHz) δ 4.17 (s, 3 H), 3.96 (s, 3 H), 2.78 (s, 1 H), 0.89 (s, 9 H), 0.26 (s, 3 H), 0.21 (s, 3 H); ^{13}C NMR (100 MHz) δ 180.0, 165.0, 135.2, 79.6, 79.2, 77.2, 59.7, 58.5, 25.5, 17.9, -3.7; IR (CH_2Cl_2) 2110, 1784, 841, 782 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{14}H_{22}NaO_4Si]^+$ (M+Na), 305.11851; found, 305.11796.

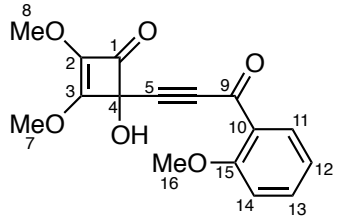
NMR Assignments. ^{1}H NMR (400 MHz) δ 4.17 (s, 3 H, C7-H), 3.96 (s, 3 H, C8-H), 2.78 (s, 1 H, C6-H), 0.89 (s, 9 H, C11-H), 0.26 (s, 3 H, C9-H), 0.21 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 180.0 (C1), 165.0 (C3), 135.2 (C2), 79.6 (C5), 79.2 (C4), 77.2 (C6), 59.7 (C7), 58.5 (C8), 25.5 (C12), 17.9 (C11), -3.7 (C9).



4-(3-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-3-oxoprop-1-ynyl)-4-hydroxy-2,3-dimethoxycyclobut-2-enone (2.23). ALN-2-46. NaH (0.12 g, 4.9 mmol) was added to a mixture of **2.11** (0.28 g, 1.6 mmol) and **2.15** (0.55 g, 2.0 mmol) in DME (16 mL). The reaction was heated under reflux for 1.5 h, and then cooled to room temperature. Stirring was continued for 15 min at which time the reaction was quenched by pouring into a separatory funnel containing Et_2O (15 mL) and saturated aqueous NH_4Cl (15 mL). The product was extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8 g silica gel) eluting with Hexanes:EtOAc (3:1) with 1% NEt_3 to afford 0.65 g (99%) of **2.23** as a below room temperature melting solid; ^{1}H NMR (400 MHz) δ 7.81-7.78 (m, 1 H), 7.42-7.37 (m, 1 H), 7.00-6.96 (m, 1 H), 6.90-6.88 (m, 1 H), 4.37 (s, 3 H), 3.71 (s, 3 H), 3.31 (s, 1 H), 0.99 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (100 MHz) δ 183.0, 182.7, 162.5, 155.9, 133.8, 131.5, 121.2, 121.1, 120.7, 112.0, 111.4, 85.1, 69.7, 61.3, 55.0, 25.6, 18.2, -4.7; IR (CH_2Cl_2) 3263, 1789, 1742, 1620, 917 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{21}H_{26}NaO_6Si]^+$ (M+Na), 425.1397; found, 425.1391.

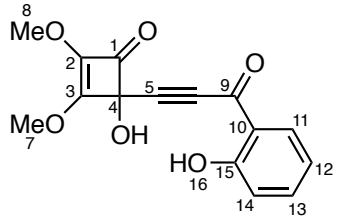
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.81-7.78 (m, 1 H, C15-H), 7.42-7.37 (m, 1 H, C13-H), 7.00-6.96 (m, 1 H, C14-H), 6.90-6.88 (m, 1 H, C12-H), 4.37 (s, 3 H, C7-H), 3.71 (s, 3 H, C8-H), 3.31 (s, 1 H, OH), 0.99 (s, 9 H, C18-H), 0.22 (s, 6 H, C16-H); ^{13}C NMR (100 MHz) δ 183.0 (C1), 182.7 (C9), 162.5 (C11), 155.9 (C3), 133.8 (C13)

131.5 (C15), 121.2 (C12), 121.1 (C2), 120.7 (C14), 112.0 (C10), 111.4 (C5), 85.1 (C6), 69.7 (C4), 61.3 (C8), 55.0 (C7), 25.6 (C18), 18.2 (C17), -4.7 (C16).



4-Hydroxy-2,3-dimethoxy-4-(3-(2-methoxyphenyl)-3-oxoprop-1-ynyl)-cyclobut-2-enone (2.24). ALN-2-82. NaH (0.39 g, 16 mmol) was added to a mixture of **2.11** (0.90 g, 5.4 mmol) and **2.16** (1.1 g, 6.4 mmol) in DME (27 mL). After evolution of hydrogen had ceased, the reaction was heated under reflux for 3 h at which time the oil bath was removed, and the reaction was cooled to room temperature. The reaction was quenched by pouring into a separatory funnel containing Et_2O (25 mL) and saturated aqueous NH_4Cl (25 mL). The product was washed with Et_2O (3 x 25 mL), and the combined organic layers were washed with brine (1 x 25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (110 g silica gel) eluting with CH_2Cl_2:MeOH (100:1) to give a colorless oil. The solid, formed upon standing, was recrystallized from CH_2Cl_2/Hexanes to afford 1.04 g (64%) of **2.24** as a colorless solid: mp 110-111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93-7.90 (m, 1 H), 7.55-7.50 (m, 1 H), 7.01-6.97 (comp, 2 H), 4.39 (s, 3 H), 3.91 (s, 3 H), 3.75 (s, 3 H), 3.30 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.9, 182.7, 162.4, 159.1, 135.0, 131.5, 120.2, 117.5, 112.8, 111.4, 111.3, 88.6, 69.8, 62.0, 55.9, 54.6; IR (CH_2Cl_2) 3259, 1786, 1735, 1045 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{16}H_{14}NaO_6]^+$ (M+Na), 325.0688; found, 325.0686.

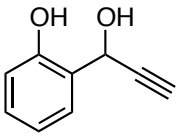
NMR Assignments. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93-7.90 (m, 1 H, C11-H), 7.55-7.50 (m, 1 H, C13-H), 7.01-6.97 (comp, 2 H, C12+C14-H), 4.39 (s, 3 H, C7-H), 3.91 (s, 3 H, C16-H), 3.75 (s, 3 H, C8-H), 3.30 (s, 1 H, C4-OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.9 (C1), 182.7 (C9), 162.4 (C15), 159.1 (C3), 135.0 (C11), 131.5 (C13), 120.2 (C12), 117.5 (C10), 112.8 (C14), 111.4 (C5), 111.3 (C2), 88.6 (C6), 69.8 (C4), 62.0 (C7), 55.9 (C16), 54.6 (C8).



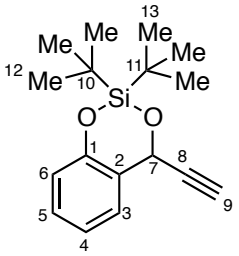
4-Hydroxy-4-(3-(2-hydroxyphenyl)-3-oxoprop-1-ynyl)-2,3-dimethoxycyclobut-2-enone (2.25). ALN-2-76. HF•pyridine complex (70% solution, 0.05 mL, 2.7 mmol) was added to a plastic centrifuge tube containing a solution of **2.23** (0.36 g, 0.89 mmol) and pyridine (0.18 g, 0.18 mL, 2.2 mmol) in THF (9 mL). The reaction was stirred at room temperature for 4 h at which time brine (10 mL) was added. The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8 g silica gel) eluting with Hexanes:EtOAc (9:1) to give a yellow oil. The solid, formed upon standing, was recrystallized from CH_2Cl_2/Hexanes to afford 0.18 g (69%) of **2.25** as a colorless solid: mp 106-107 °C; ^{1}H NMR (400 MHz) δ 10.27 (s, 1 H), 7.88 (d, J = 7.6 Hz, 1 H), 7.50 (t, J = 7.6 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.91 (t, J = 7.6 Hz), 4.42 (s, 3 H), 3.75 (s, 3 H), 3.36 (s, 1 H); ^{13}C NMR (100 MHz) δ 182.1, 181.8, 167.5, 162.1, 136.7, 130.2, 119.4, 117.8, 112.6, 112.1, 111.2, 85.8, 69.4, 61.6, 55.4; IR (CH_2Cl_2) 3264,

1789, 1687, 1616, 1365 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{15}H_{12}O_6Na]^+$ (M+Na), 311.05316; found, 311.05261.

NMR Assignments. ^1H NMR (400 MHz) δ 10.27 (s, 1 H, C15-OH), 7.88 (d, *J* = 7.6 Hz, 1 H, C11-H), 7.50 (t, *J* = 7.6 Hz, 1 H, C13-H), 6.99 (d, *J* = 7.6 Hz, 1 H, C14-H), 6.91 (t, *J* = 7.6 Hz, C12-H), 4.42 (s, 3 H, C7-H), 3.75 (s, 3 H, C8-H), 3.36 (s, 1 H, C4-OH); ^{13}C NMR (100 MHz) δ 182.1 (C1), 181.9 (C9), 167.5 (C15), 162.1 (C2), 136.6 (C11), 130.2 (C13), 119.4 (C12), 117.8 (C14), 112.6 (C2), 112.1 (C10), 111.2 (C5), 85.8 (C6), 69.4 (C4), 61.6 (C7), 55.4 (C8).



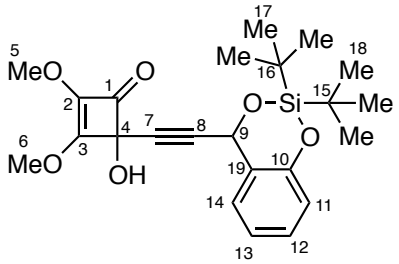
2-(1-Dihydroxyprop-2-yn-1-yl)phenol (2.37). ALN-2-132. Prepared according to literature procedures.[274]



2,2-Di-*tert*-butyl-4-ethynyl-4*H*-benzo[*d*][1,3,2]dioxasiline (2.39). ALN-2-279. Freshly distilled 2,6-lutidine (2.5 g, 2.7 mL, 24 mmol) was added to a solution of **2.37** (1.4 g, 9.4 mmol) in CH_2Cl_2 (25 mL) at 0 ˚C. After stirring for 5 min, di(*tert*-butyl)silyl bis(triflate) (3.6 mL, 4.9 g, 11 mmol) was added, and the reaction was stirred at 0 ˚C for 3 h. The reaction was diluted with saturated aqueous NH_4Cl (15 mL), the ice bath was removed, and the aqueous mixture was washed with CH_2Cl_2 (3 x 15 mL). The combined

organic layers were washed with brine (1 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (20:1) to give 2.7 g (99%) of **2.39** as a yellow oil; ^{1}H NMR (400 MHz, C_6D_6) δ 7.39 (d, *J* = 8.0 Hz, 1 H), 7.02-6.94 (comp, 2 H), 6.78 (td, *J* = 8.0, 1.2 Hz, 1 H), 5.89 (d, *J* = 2.0 Hz, 1 H), 2.19 (d, *J* = 2.0 Hz, 1 H), 1.08 (s, 9 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz) δ 153.3, 129.6, 126.8, 126.1, 121.0, 119.5, 82.7, 74.4, 64.7, 26.94, 26.87, 21.6, 20.9; IR (CH_2Cl_2) 3073, 2936, 2126, 1186 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{24}O_2Si]^+$ (M+H), 288.1546; found, 288.1539.

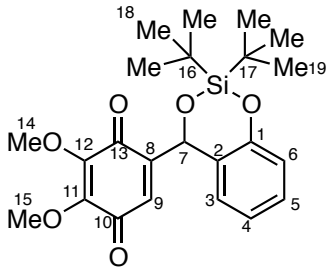
NMR Assignments. ^{1}H NMR (400 MHz, C_6D_6) δ 7.39 (d, *J* = 8.0 Hz, 1 H, C3-H), 7.02-6.94 (comp, 2 H, C4+C5-H), 6.78 (td, *J* = 8.0, 1.2 Hz, 1 H), 5.89 (d, *J* = 2.0 Hz, 1 H, C7-H), 2.19 (d, *J* = 2.0 Hz, 1 H, C9-H), 1.08 (s, 9 H, C12/C13), 1.04 (s, 9 H, C12/C13); ^{13}C NMR (100 MHz) δ 153.3 (C1), 129.6 (C5), 126.8 (C3), 126.1 (C2), 121.0 (C4), 119.5 (C6), 82.7 (C8), 74.4 (C9), 64.7 (C7), 26.9 (C10+C11), 21.6 (C10/C11), 20.9 (C10/C11).



4-((2,2-Di-*tert*-butyl-4*H*-benzo[*d*][1,3,2]dioxasilin-4-yl)ethynyl)-4-hydroxy-2,3-dimethoxycyclobut-2-enone (2.40). ALN-3-36. *n*-BuLi (1.3 mL, 2.7 mmol, 2.12 M in Hexanes) was added to a solution of **2.39** (0.78 g, 2.7 mmol) in THF (15 mL) at -78 ˚C. After stirring for 30 min, a solution of **2.9** (0.32 g, 2.3 mmol) in THF (8 mL) at -78 ˚C was transferred *via* cannula to the acetylide solution. After stirring for 1 h, AcOH (1

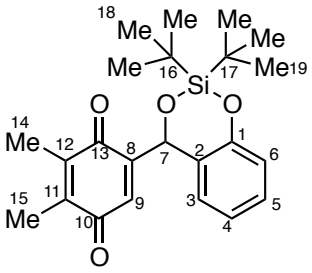
M in THF, 10 mL) was added, the cooling bath was removed, and the reaction was warmed to room temperature over 30 min. The reaction was concentrated under reduced pressure, diluted with Et_2O (~30 mL), vacuum filtered, and then again concentrated under reduced pressure to obtain **2.40** as a mixture of diastereomers; ^{1}H NMR (500 MHz, C_6D_6) δ 7.54-7.49 (m, 1 H), 7.00-6.91 (comp, 2 H), 6.85-6.79 (m, 1 H), 6.01 (s, 0.5 H), 5.96 (s, 0.5 H), 3.67 (br s, 0.5 H), 3.60 (br s, 0.5 H), 3.53 (s, 3 H), 3.44 (s, 1.5 H), 3.42 (s, 1.5 H), 1.07 (s, 4.5 H), 1.07 (s, 4.5 H), 1.03 (s, 4.5 H), 1.02 (s, 4.5 H); ^{13}C NMR (125 MHz, C_6D_6) δ 180.6, 180.3, 164.5, 164.4, 153.8., 153.7, 135.9, 135.8, 130.0, 127.6, 127.5, 126.6 x 2, 121.7 x 2, 119.8 x 2, 88.3, 88.2, 81.9 x 2, 79.2 x 2, 65.9, 65.5, 59.5, 59.4, 58.1 x 2, 27.1, 27.0 x 2, 21.7 x 2, 21.1; HRMS (CI) *m/z* calculated for $[C_{23}H_{31}O_6Si]^+$ (M+H), 431.1890; found, 431.1882.

NMR Assignments. ^{1}H NMR (500 MHz, C_6D_6) δ 7.54-7.49 (m, 1 H, C14-H), 7.00-6.91 (comp, 2 H, C11+C12-H), 6.85-6.79 (m, 1 H, C13-H), 6.01 (s, 0.5 H, C9-H), 5.96 (s, 0.5 H, C9-H), 3.67 (br s, 0.5 H, C4-OH), 3.60 (br s, 0.5 H, C4-OH), 3.53 (s, 3 H, C6-H), 3.44 (s, 1.5 H, C5-H), 3.42 (s, 1.5 H, C5-H), 1.07 (s, 4.5 H, C17/C18-H), 1.07 (s, 4.5 H, C17/C18-H), 1.03 (s, 4.5 H, C17/C18-H), 1.02 (s, 4.5 H, C17/C18-H); ^{13}C NMR (125 MHz, C_6D_6) δ 180.6 (C1), 180.3 (C1), 164.5 (C3), 164.4 (C3), 153.8 (C10), 153.7 (C10), 135.9 (C2), 135.8 (C2), 130.0 (C12), 127.6 (C14), 127.5 (C14), 126.6 x 2 (C19), 121.7 x 2 (C13), 119.8 x 2 (C11), 88.3 (C4), 88.2 (C4), 81.9 x 2 (C7), 79.2 x 2 (C8), 65.9 (C9), 65.5 (C9), 59.5 (C6), 59.4 (C6), 58.1 x 2 (C5), 27.1 (C17), 27.0 x 2 (C18), 21.7 x 2 (C15/C16), 21.1 (C15/C16).



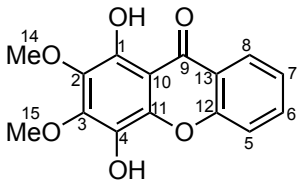
5-(2,2-Di-*tert*-butyl-4*H*-benzo[*d*][1,3,2]dioxasilin-4-yl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.44). ALN-3-36. The resulting oil **2.40** was dissolved in $PhCH_3$ (20 mL), degassed with Ar for 20 min, and then heated under reflux for 12 h. The reaction was cooled to ambient temperature, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (20:1 to 10:1) to afford 0.59 g (61% over two steps) of **2.44** as a solid that melts at room temperature; ^{1}H NMR (400 MHz) δ 7.20 (t, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 6.83 (t, *J* = 8.0 Hz, 1 H), 6.62 (s, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 6.20 (s, 1 H), 4.07 (s, 3 H), 4.05 (s, 3 H), 1.10 (s, 9 H), 0.96 (s, 9 H); ^{13}C NMR (100 MHz) δ 184.3, 183.5, 154.2, 147.5, 145.0, 144.7, 132.1, 129.5, 128.0, 126.6, 119.7, 68.6, 61.4, 61.3, 27.1, 27.0, 21.7, 21.1; IR (CH_2Cl_2) 2932, 2859, 1658, 1604, 1482, 1455, 1247 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{23}H_{31}O_6Si]^+$ (M+H), 431.1890; found, 431.1892.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.20 (t, *J* = 8.0 Hz, 1 H, C5-H), 6.96 (d, *J* = 8.0 Hz, 1 H, C3-H), 6.83 (t, *J* = 8.0 Hz, 1 H, C4-H), 6.62 (s, 1 H, C9-H), 6.55 (d, *J* = 8.0 Hz, 1 H, C6-H), 6.20 (s, 1 H, C7-H), 4.07 (s, 3 H, C14/C15-H), 4.05 (s, 3 H, C14/C15-H), 1.10 (s, 9 H, C18/C19-H), 0.96 (s, 9 H, C18/C19-H); ^{13}C NMR (100 MHz) δ 184.3 (C10), 183.5 (C13), 154.2 (C1), 147.5 (C8), 145.0 (C11/C12), 144.7 (C11/C12), 132.1 (C9), 129.5 (C5), 128.0 (C2), 126.6 (C6), 121.0 (C4), 119.7 (C3), 68.6 (C7), 61.4 (C14/C15), 61.3 (C14/C15), 27.1 (C16+C17), 21.7 (C18/C19), 21.1 (C18/C19).



5-(2,2-Di-*tert*-butyl-4*H*-benzo[*d*][1,3,2]dioxasilin-4-yl)-2,3-dimethylcyclohexa-2,5-diene-1,4-dione (2.47) ALN-3-72. Setup as above, except squarate **2.45** was used instead of **2.9**. The crude product mixture was purified by flash column chromatography eluting with Hexanes:EtOAc (30:1) to afford 0.78 g (63% over 2 steps) of **2.47** as a red oil; ^{1}H NMR (500 MHz) δ 7.17 (app td, *J* = 8.0, 1.7 Hz, 1 H), 6.94 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.79 (app td, *J* = 8.0, 1.2 Hz, 1 H), 6.74 (d, *J* = 1.2 Hz, 1 H), 6.50 (app d, *J* = 7.9 Hz, 1 H), 6.22 (s, 1 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.09 (s, 9 H), 0.95 (s, 9 H); ^{13}C NMR (125 MHz) δ 187.8, 186.9, 154.3, 148.7, 141.0, 140.9, 133.7, 129.3, 128.4, 126.6, 120.9, 119.6, 68.7, 27.1, 27.0, 21.8, 21.1, 12.5, 12.2; IR (CH_2Cl_2) 2924, 2855, 1651, 1618, 1483, 1454, 827 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{23}H_{31}O_4Si]^+$ (M+H), 399.1992; found, 399.1992.

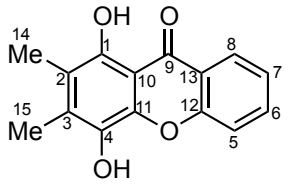
NMR Assignments. ^{1}H NMR (500 MHz) δ 7.17 (app td, *J* = 8.0, 1.7 Hz, 1 H, C3-H), 6.94 (dd, *J* = 8.0, 1.2 Hz, 1 H, C2-H), 6.79 (app td, *J* = 8.0, 1.2 Hz, 1 H, C4-H), 6.74 (d, *J* = 1.2 Hz, 1 H, C9-H), 6.50 (app d, *J* = 7.9 Hz, 1 H, C5-H), 6.22 (s, 1 H, C7-H), 2.09 (s, 3 H, C14-H), 2.05 (s, 3 H, C15-H), 1.09 (s, 9 H, C18/C19-H), 0.95 (s, 9 H, C18/C19-H); ^{13}C NMR (125 MHz) δ 187.8 (C13), 186.9 (C10), 154.3 (C1), 148.7 (C8), 141.0 (C11/C12), 140.9 (C11/C12), 133.7 (C9), 129.3 (C3), 128.4 (C6), 126.6 (C5), 120.9 (C4), 119.6 (C2), 68.7 (C7), 27.1 (C18/C19), 27.0 (C18/C19), 21.8 (C16/C17), 21.1 (C16/C17), 12.5 (C14), 12.2 (C15).



1,4-Dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (2.27a). ALN-3-74. HF•pyridine (70% HF, 0.004 mL, 0.18 mmol), was added to a stirred solution of **2.44** (0.031 g, 0.072 mmol) and pyridine (0.017 g, 0.017 mL, 0.22 mmol) in THF (4 mL) in a plastic reaction vessel at ambient temperature. After stirring for 1 h, Et_2O (10 mL) was added, and the solution was washed with brine (1 x 10 mL). The brine was extracted with Et_2O (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was dissolved in acetone (10 mL) and cooled to 0 ˚C. A solution of Jones reagent (0.14 mL, 0.22 mmol, 1.5 M) was added to the reaction, and the green solution was stirred for 1 h at which time EtOH (1 mL) and saturated aqueous $NaHCO_3$ (10 mL) were added. The aqueous layer was washed with Et_2O (3 x 12 mL), and the combined organic layers were washed with brine (1 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by filtering through a plug of silica gel eluting with CH_2Cl_2:MeOH (10:1) to provide 0.014 g (67% over two steps) of **2.44** as a yellow solid (Et_2O/Hexanes): mp 180-181 ˚C; ^{1}H NMR (400 MHz) δ 12.39 (s, 1 H), 8.27 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.75 (td, *J* = 8.0, 2.0 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 5.43 (s, 1 H), 4.19 (s, 3 H), 3.98 (s, 3 H); ^{13}C NMR (100 MHz) δ 181.7, 156.0, 148.0, 147.1, 139.4, 135.4, 134.8, 128.7, 126.0, 124.1, 120.1, 117.9, 105.2, 61.7, 61.1; IR (CH_2Cl_2) 3385, 2922, 2851, 1651, 1464 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{13}O_6]^+$ (M+H), 289.0712; found, 289.0713.

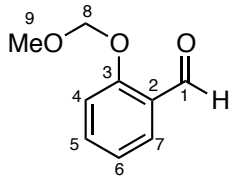
NMR Assignments. ^{1}H NMR (400 MHz) δ 12.39 (s, 1 H, C1-OH), 8.27 (dd, *J* = 7.8, 1.2 Hz, 1 H, C8-H), 7.75 (td, *J* = 8.0, 2.0 Hz, 1 H, C6-H), 7.56 (d, *J* = 7.6 Hz, 1 H,

C5-H), 7.40 (t, *J* = 8.0 Hz, 1 H, C7-H), 5.43 (s, 1 H, C4-OH), 4.19 (s, 3 H, C15), 3.98 (s, 3 H, C14); ^{13}C NMR (100 MHz) δ 181.7 (C9), 156.0 (C12), 148.0 (C11), 147.1 (C3), 139.4 (C1), 135.4 (C6), 134.8 (C2), 128.7 (C4), 126.0 (C8), 124.1 (C7), 120.1 (C13), 117.9 (C5), 105.2 (C10), 61.7 (C15), 61.1 (C14).

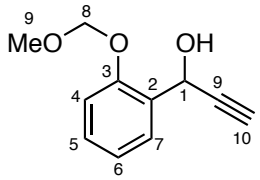


1,4-Dihydroxy-2,3-dimethyl-9*H*-xanthen-9-one (2.49). ALN-3-76. Setup as for **2.27a**. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford 0.008 g (57% over two steps) of **2.49** as a yellow solid (Hexanes/Et_2O): mp 265-266 °C (dec.); ^{1}H NMR (400 MHz) δ 12.39 (s, 1 H), 8.30 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.75 (t, *J* = 7.2 Hz, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 7.2 Hz, 1 H), 5.26 (s, 1 H), 2.37 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR (100 MHz) δ 181.6, 155.7, 151.5, 140.5, 135.2, 133.9, 133.5, 126.4, 124.1, 120.8, 118.4, 117.5, 106.3, 13.1, 10.8; IR (CH_2Cl_2) 3360, 2923, 2852, 1650 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{13}O_4]^+$ (M+H), 257.0809; found, 257.0809.

NMR Assignments. ^{1}H NMR (400 MHz) δ 12.39 (s, 1 H, C1-OH), 8.30 (dd, *J* = 8.4, 1.6 Hz, 1 H, C8-H), 7.75 (t, *J* = 7.2 Hz, 1 H, C6-H), 7.50 (d, *J* = 8.0 Hz, 1 H, C5-H), 7.41 (t, *J* = 7.2 Hz, 1 H, C7-H), 5.26 (s, 1 H, C4-OH), 2.37 (s, 3 H, C15-H), 2.24 (s, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 181.6 (C9), 155.7 (C12), 151.5 (C1), 140.5 (C11), 135.2 (C6), 133.9 (C3), 133.5 (C4), 126.4 (C8), 124.1 (C7), 120.8 (C13), 118.4 (C2), 117.5 (C5), 106.3 (C10), 13.1 (C15), 10.8 (C14).

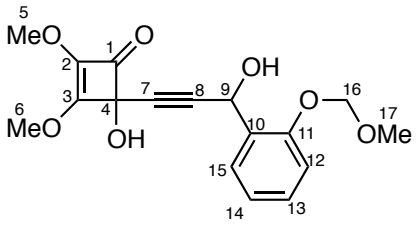


2-(Methoxymethoxy)benzaldehyde (2.60). ALN-3-156. Prepared according to literature procedures.[274]



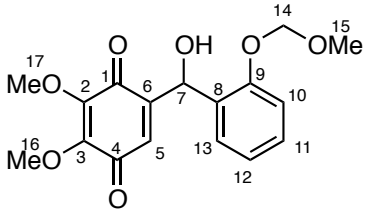
1-(2-(Methoxymethoxy)phenyl)prop-2-yn-1-ol (2.61). ALN-3-218. A solution of **2.36** (33 mL, 17 mmol, 0.5 M in THF) was added to a solution of **2.60** (2.3 g, 14 mmol) in THF (80 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 4 h and then quenched with the addition of saturated aqueous NH_4Cl (50 mL). The aqueous layer was washed with Et_2O (3 x 20 mL), and the combined organic layers were washed with brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by filtering through a short plug of silica gel eluting with Hexanes:EtOAc (1:1) to deliver 2.4 g (88%) of **2.61** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.47 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.20 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.95 (td, *J* = 7.6, 1.6 Hz, 1 H), 5.60 (dd, *J* = 7.0, 2.0 Hz, 1 H), 5.17 (s, 2 H), 3.41 (s, 3 H), 2.84 (d, *J* = 6.4 Hz, 1 H), 2.51 (s, 1 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.47 (dd, *J* = 7.6, 1.6 Hz, 1 H, C7-H), 7.20 (td, *J* = 7.6, 1.6 Hz, 1 H, C5-H), 7.04 (dd, *J* = 7.6, 1.6 Hz, 1 H, C4-H), 6.95 (td, *J* = 7.6, 1.6 Hz, 1 H, C6-H), 5.60 (dd, *J* = 7.0, 2.0 Hz, 1 H, C1-H), 5.17 (s, 2 H, C8-H), 3.41 (s, 3 H, C9-H), 2.84 (d, *J* = 6.4 Hz, 1 H, C1-OH), 2.51 (s, 1 H, C10-H).



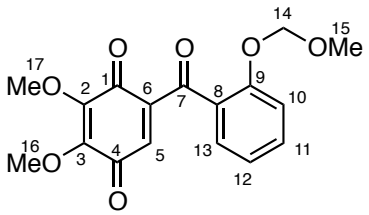
4-Hydroxy-4-(3-hydroxy-3-(2-(methoxymethoxy)phenyl)prop-1-yn-1-yl)-2,3-dimethoxycyclobut-2-enone (2.62). ALN-3-250. NaH (0.10 g, 2.6 mmol, 60% dispersion in mineral oil) was added to a solution of **2.61** (0.45 g, 2.3 mmol) in DME (10 mL) at 0 ˚C. After 15 min, a solution of *n*-BuLi (1.5 mL, 2.6 mmol, 1.71 M in Hexanes) was added dropwise. The red reaction mixture was stirred for 15 min at 0 ˚C whereupon a solution of **2.9** (0.67 g, 4.7 mmol) in DME (13 mL) was added dropwise *via* addition funnel over 5 min. The reaction was stirred for 25 min, whereupon saturated aqueous NH_4Cl (10 mL) and H_2O (10 mL) were added. The combined aqueous layers were washed with Et_2O (6 x 15 mL), and the combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (2:1 to 1:1) to afford 0.49 g (62%) of **2.62** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.52-7.49 (m, 1 H), 7.31-7.27 (m, 1 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 7.03 (t, *J* = 8.4 Hz, 1 H), 5.74 (br s, 1 H), 5.25 (s, 2 H), 4.17 (s, 3 H), 3.94 (s, 3 H), 3.72 (br s, 1 H), 3.50 (s, 3 H), 3.48 (br s 1 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.52-7.49 (m, 1 H, C15-H), 7.31-7.27 (m, 1 H, C13-H), 7.11 (d, *J* = 8.4 Hz, 1 H, C12-H), 7.03 (t, *J* = 8.4 Hz, 1 H, C14-H), 5.74 (br s, 1 H, C9-H), 5.25 (s, 2 H, C16-H), 4.17 (s, 3 H, C6-H), 3.94 (s, 3 H, C5-H), 3.72 (br s, 1 H, C4-OH), 3.50 (s, 3 H, C17-H), 3.48 (br s 1 H, C9-OH).



5-(Hydroxy(2-(methoxymethoxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.63). ALN-3-163. A solution of **2.62** (0.016 g, 0.048 mmol) in THF (4.8 mL) was sparged with Ar for 15 min. The reaction was then placed in a microwave oven and heated at 120 ˚C for 35 min. The reaction was cooled to room temperature, concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1 to 1:1) to deliver 0.015 g (94%) of **2.63** as a red oil; ^{1}H NMR (400 MHz) δ 7.37 (d, *J* = 7.6 Hz, 1 H), 7.27 (m, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 7.03 (t, *J* = 7.6 Hz, 1 H), 6.48 (s, 1 H), 6.07 (d, *J* = 5.6 Hz, 1 H), 5.21 (s, 2 H), 4.02 (s, 3 H), 3.98 (s, 3 H), 3.45 (s, 3 H), 3.25 (d, *J* = 5.6 Hz, 1 H).

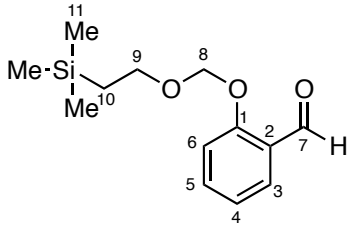
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.37 (d, *J* = 7.6 Hz, 1 H, C10-H), 7.27 (m, 1 H, C12-H), 7.10 (d, *J* = 7.6 Hz, 1 H, C13-H), 7.03 (t, *J* = 7.6 Hz, 1 H, C12-H), 6.48 (s, 1 H, C5-H), 6.07 (d, *J* = 5.6 Hz, 1 H, C7-H), 5.21 (s, 2 H, C14-H), 4.02 (s, 3 H, C16-H), 3.98 (s, 3 H, C17-H), 3.45 (s, 3 H, C15-H), 3.25 (d, *J* = 5.6 Hz, 1 H, C7-OH).



2,3-Dimethoxy-5-(2-(methoxymethoxy)benzoyl)cyclohexa-2,5-diene-1,4-dione (2.64). ALN-3-168. A solution of Jones reagent (0.038 mL, 0.10 mmol, 2.67 M) was

added to a stirred solution of **2.63** (0.028 g, 0.084 mmol) in acetone at 0 ˚C. The reaction was stirred for 1.5 h whereupon 2-propanol (~0.5 mL) was added. The reaction was warmed to room temperature and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was washed with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to deliver 0.028 g (99%) of **2.64** as a red oil. The reaction provided analytically pure product, no purification was necessary; ^{1}H NMR (400 MHz) δ 7.90 (d, *J* = 6.0 Hz, 1 H), 7.53 (t, *J* = 6.0 Hz, 1 H), 7.16-7.10 (comp, 2 H), 6.60 (s, 1 H), 5.09 (s, 2 H), 4.07 (s, 3 H), 4.01 (s, 3 H), 3.35 (s, 3 H); IR (CH_2Cl_2) 2918, 1655, 1596, 1455, 968 cm^{-1}.

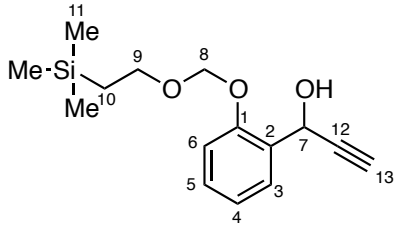
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.90 (d, *J* = 6.0 Hz, 1 H, C13-H), 7.53 (t, *J* = 6.0 Hz, 1 H, C11-H), 7.16-7.10 (comp, 2 H, C10+C12-H), 6.60 (s, 1 H, C5-H), 5.09 (s, 2 H, C14-H), 4.07 (s, 3 H, C16-H), 4.01 (s, 3 H, C17-H), 3.35 (s, 3 H, C15-H).



2-((2-(Trimethylsilyl)ethoxy)methoxy)benzaldehyde (2.67). ALN-3-210. K_2CO_3 (1.5 g, 11 mmol) was added to a solution of **2.35a** (0.33 g, 0.29 mL, 2.7 mmol) in DMF (5 mL) at ambient temperature. The reaction was stirred for 5 min whereupon a solution of SEM-Cl (0.72 g, 4.3 mmol) in DMF (5 mL) was added. The reaction was stirred at room temperature for 24 h, and then in a 45 ˚C oil bath for 48 h until consumption of **2.35a** was indicated by TLC. The reaction was diluted with H_2O (15

mL), and the aqueous layer was washed with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by filtering through a short silica gel plug eluting with Hexanes:EtOAc (1:1) to deliver 0.68 g (99%) of **2.67** as a yellow oil; ^{1}H NMR (400 MHz) δ 10.50 (s, 1 H), 7.84 (dd, *J* = 7.4, 2.0 Hz, 1 H), 7.53 (td, *J* = 7.4, 2.0 Hz, 1 H), 7.25 (m, 1 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 5.35 (s, 2 H), 3.80 (comp, 2 H), 0.97 (comp, 2 H), 0.01 (s, 9 H).

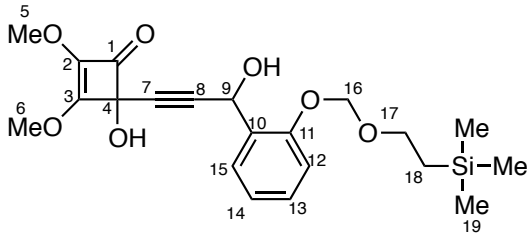
NMR Assignments. ^{1}H NMR (400 MHz) δ 10.50 (s, 1 H, C7-H), 7.84 (dd, *J* = 7.4, 2.0 Hz, 1 H, C3-H), 7.53 (td, *J* = 7.4, 2.0 Hz, 1 H, C5-H), 7.25 (m, 1 H, C6-H), 7.08 (t, *J* = 7.4 Hz, 1 H, C4-H), 5.35 (s, 2 H, C8-H), 3.80 (comp, 2 H, C9-H), 0.97 (comp, 2 H, C10-H), 0.01 (s, 9 H, C11-H).



1-(2-((2-(Trimethylsilyl)ethoxy)methoxy)phenyl)prop-2-yn-1-ol (2.68). ALN-3-213. Ethynyl magnesium bromide (6.5 mL, 3.2 mmol, 0.5 M in THF) was added to a solution of **2.67** (0.68 g, 2.7 mmol) in THF (27 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 2 h whereupon saturated aqueous NH_4Cl (25 mL) was added. The layers were separated, and the aqueous layer was washed with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (1 x 25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by filtering through a plug of silica gel eluting with Hexanes:EtOAc (1:1) to afford 0.47 g (63%) of **2.68** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.57 (d, *J* = 6.4 Hz, 1 H), 7.30 (t, *J* = 6.4 Hz, 1 H),

7.15 (d, *J* = 6.4 Hz, 1 H), 7.04 (t, *J* = 6.4 Hz, 1 H), 5.68 (dd, *J* = 6.6, 2.0 Hz, 1 H), 5.31 (s, 2 H), 3.78 (comp, 2 H), 3.03 (d, *J* = 6.4 Hz, 1 H), 2.60 (s, 1 H), 0.96 (comp, 2 H), 0.02 (s, 9 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.57 (d, *J* = 6.4 Hz, 1 H, C3-H), 7.30 (t, *J* = 6.4 Hz, 1 H, C5-H), 7.15 (d, *J* = 6.4 Hz, 1 H, C6-H), 7.04 (t, *J* = 6.4 Hz, 1 H, C4-H), 5.68 (dd, *J* = 6.6, 2.0 Hz, 1 H, C7-H), 5.31 (s, 2 H, C8-H), 3.78 (comp, 2 H, C9-H), 3.03 (d, *J* = 6.4 Hz, 1 H, C7-OH), 2.60 (s, 1 H, C13-H), 0.96 (comp, 2 H, C10-H), 0.02 (s, 9 H, C11-H).

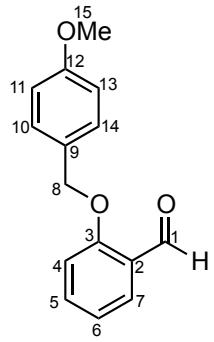


4-Hydroxy-4-(3-hydroxy-3-(2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl) prop-1-yn-1-yl)-2,3-dimethoxycyclobut-2-enone (2.69). ALN-3-160. Ethyl magnesium bromide (0.56 mL, 1.4 mmol, 2.5 M in THF) was added to a solution of **2.68** (0.19 g, 0.68 mmol) in THF (8 mL) at 0 ˚C. The solution was stirred at 0 ˚C for 15 min, and then at room temperature for 1 h. The reaction was cooled to 0 ˚C and to the anion was added a solution of **2.9** (0.081 g, 0.57 mmol) in THF (7 mL) *via* cannula. The reaction was stirred at 0 ˚C for 30 min and then room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and H_2O (5 mL). The aqueous layers were washed with Et_2O (3 x 15 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (2:1 to 1:1) to afford 0.061 g (25%) of **2.69** as a yellow oil; ^{1}H NMR

(400 MHz) δ 7.50 (d, *J* = 7.2 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.15 (d, *J* = 7.2 Hz, 1 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 5.74 (br s 1 H), 5.29 (d, *J* = 2.4 Hz, 2 H), 4.18 (s, 3 H), 3.97 (s, 3 H), 3.78 (comp, 2 H), 3.01 (comp, 2 H), 0.97 (comp, 2 H), 0.01 (s, 9 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.50 (d, *J* = 7.2 Hz, 1 H, C15-H), 7.30 (t, *J* = 7.2 Hz, 1 H, C13-H), 7.15 (d, *J* = 7.2 Hz, 1 H, C12-H), 7.04 (t, *J* = 7.2 Hz, 1 H, C14-H), 5.74 (br s 1 H, C9-H), 5.29 (d, *J* = 2.4 Hz, 2 H, C16-H), 4.18 (s, 3 H, C6-H), 3.97 (s, 3 H, C5-H), 3.78 (comp, 2 H, C17-H), 3.01 (comp, 2 H, C4-OH+C9-OH), 0.97 (comp, 2 H, C18-H), 0.01 (s, 9 H, C19-H).

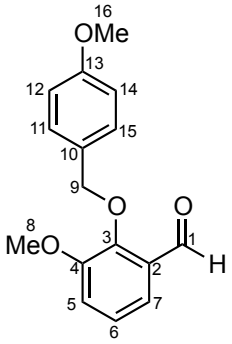
Representative Procedure for Preparation of Protected Salicylaldehydes 2.72a–i.



2-(4-Methoxybenzyloxy)benzaldehyde (2.72a). ALN-3-216. Anhydrous K_2CO_3 (39.0 g, 283 mmol) was added to a stirred solution of **2.35a** (11.5 g, 10.0 mL, 94.2 mmol) and PMB-Cl (19.2 g, 16.6 mL, 122 mmol) in DMF (95 mL) at 0 ˚C. The mixture was stirred at 0 ˚C for 1 h and then warmed to room temperature. The mixture was stirred for 20 h, whereupon the reaction was partitioned between H_2O (200 mL) and $PhCH_3$ (100 mL). The layers were separated, and the aqueous layer was washed with $PhCH_3$ (2 x 50 mL). The combined organic layers were washed with brine (1 x 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 20.7 g (91%)

of **2.72a** (colorless solid from Hexanes/EtOAc): mp 86-87 °C; ^{1}H NMR (400 MHz) δ 10.52 (s, 1 H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.54 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.08-6.94 (comp, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 5.12 (s, 2 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.8, 161.1, 159.6, 135.8, 129.1, 128.3, 128.0, 125.1, 120.9, 114.1, 113.0, 70.3, 55.3; IR (CH_2Cl_2) 2837, 1687, 1598, 1245 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{14}O_3]^{+\bullet}$ ($M^{+\bullet}$), 242.0942; found, 242.0942.

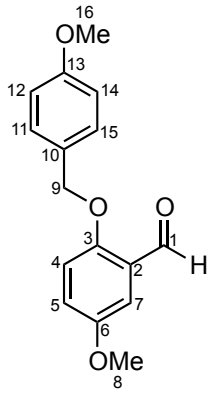
NMR Assignments. ^{1}H NMR (400 MHz) δ 10.52 (s, 1 H, C1-H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1 H, C7-H), 7.54 (dt, *J* = 8.0, 2.0 Hz, 5 H), 7.37 (d, *J* = 8.0 Hz, 2 H, C10+C14-H), 7.08-6.94 (comp, 2 H, C4/C6-H), 6.93 (d, *J* = 8.0 Hz, 2 H, C11+13-H), 5.12 (s, 2 H, C8-H), 3.83 (s, 3 H, C15-H); ^{13}C NMR (100 MHz) δ 189.8 (C1), 161.1 (C3), 159.6 (C12), 135.8 (C5), 129.1 (C10+C14), 128.3 (C7), 128.0 (C9), 125.1 (C2), 120.9 (C6), 114.1 (C11+C13), 113.0 (C4), 70.3 (C8), 55.3 (C15).



3-Methoxy-2-(4-methoxybenzyloxy)benzaldehyde (2.72b). ALN-3-282. Colorless needles from Hexanes/EtOAc (98%): mp 42-43 °C; ^{1}H NMR (400 MHz) δ 10.19 (s, 1 H), 7.37 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.17 (dd, *J* = 7.6, 2.0 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 5.12 (s, 2 H), 3.95 (s, 3 H), 3.80 (s, 3 H); ^{13}C NMR (100 MHz) δ 190.3, 159.8, 153.0, 150.9, 130.4, 130.3, 128.4,

124.1, 118.9, 117.9, 113.9, 75.9, 56.0, 55.2; IR (CH_2Cl_2) 2959, 2838, 1690, 1250 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{15}O_4]^-$ (M-H), 271.0970; found, 271.0970.

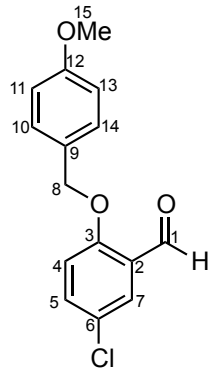
NMR Assignments. ^{1}H NMR (400 MHz) δ 10.19 (s, 1 H, C1-H), 7.37 (dd, *J* = 7.6, 2.0 Hz, 1 H, C7-H), 7.28 (d, *J* = 8.8 Hz, 2 H, C11+C15-H), 7.17 (dd, *J* = 7.6, 2.0 Hz, 1 H, C5-H), 7.13 (t, *J* = 7.6 Hz, 1 H, C6-H), 6.87 (d, *J* = 8.8 Hz, 2 H, C12+C14-H), 5.12 (s, 2 H, C9-H), 3.95 (s, 3 H, C8-H), 3.80 (s, 3 H, C16-H); ^{13}C NMR (100 MHz) δ 190.3 (C1), 159.8 (C13), 153.0 (C4), 150.9 (C3), 130.4 (C11+C15), 130.3 (C7), 128.4 (C10), 124.1 (C5), 118.9 (C2), 117.9 (C6), 113.9 (C12+C14), 75.9 (C9), 56.0 (C8), 55.2 (C16).



5-Methoxy-2-(4-methoxybenzyloxy)benzaldehyde (2.72c). ALN-4-188. Beige powder from Hexanes/EtOAc (80%): mp 73-74 °C; ^{1}H NMR (400 MHz) δ 10.46 (s, 1 H), 7.34-7.32 (comp, 3 H), 7.11 (dd, *J* = 9.0, 3.2 Hz, 1 H), 7.00 (d, *J* = 9.0 Hz, 1 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 5.06 (s, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.5, 159.5, 153.7, 129.1, 128.1, 125.5, 123.3, 115.2, 114.0, 110.0, 71.1, 55.7, 55.2; IR (CH_2Cl_2) 2937, 2836, 1682, 1493, 1216, 820 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{16}O_4]^{+\bullet}$ ($M^{+\bullet}$), 272.1049; found, 272.1046.

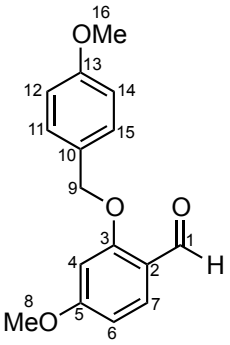
NMR Assignments. ^{1}H NMR (400 MHz) δ 10.46 (s, 1 H, C1-H), 7.34-7.32 (comp, 3 H, C11+C25-H/C7-H), 7.11 (dd, *J* = 9.0, 3.2 Hz, 1 H, C5-H), 7.00 (d, *J* = 9.0

Hz, 1 H, C4-H), 6.91 (d, *J* = 8.6 Hz, 2 H, C12+C14-H), 5.06 (s, 2 H, C9-H), 3.81 (s, 3 H, C16-H), 3.78 (s, 3 H, C8-H); ^{13}C NMR (100 MHz) δ 189.5 (C1), 159.5 (C6), 155.8 (C3), 153.7 (C13), 129.1 (C11+C15), 128.1 (C10), 125.5 (C2), 123.3 (C5), 115.2 (C4), 114.0 (C12+C14), 110.0 (C7), 71.1 (C9), 55.7 (C8), 55.2 (C16).



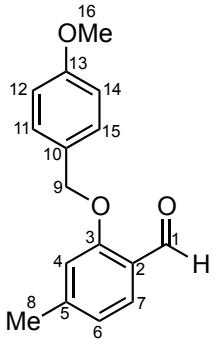
5-Chloro-2-(4-methoxybenzyloxy)benzaldehyde (2.72d). ALN-4-26. Colorless plates from Hexanes/EtOAc (78%): mp 98-99 °C; ^{1}H NMR (400 MHz) δ 10.44 (s, 1 H), 7.79 (d, *J* = 2.8 Hz, 1 H), 7.47 (dd, *J* = 8.9, 2.8 Hz, 1 H), 7.34 (d, *J* = 8.7 Hz, 2 H), 7.02 (d, *J* = 8.9 Hz, 1 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 5.11 (s, 2 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz) δ 188.5, 159.8, 159.5, 135.3, 129.1, 127.9, 127.5, 126.6, 126.0, 114.8, 114.1, 70.8, 55.3; IR (CH_2Cl_2) 2913, 1680, 1239, 831 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{13}O_3Cl]^{+\bullet}$ ($M^{+\bullet}$), 276.0553; found, 276.0552.

NMR Assignments. ^{1}H NMR (400 MHz) δ 10.44 (s, 1 H, C1-H), 7.79 (d, *J* = 2.8 Hz, 1 H, C7-H), 7.47 (dd, *J* = 8.9, 2.8 Hz, 1 H, C5-H), 7.34 (d, *J* = 8.7 Hz, 2 H, C10+C14-H), 7.02 (d, *J* = 8.9 Hz, 1 H, C4-H), 6.93 (d, *J* = 8.7 Hz, 2 H, C11+C13-H), 5.11 (s, 2 H, C8-H), 3.83 (s, 3 H, C15-H); ^{13}C NMR (100 MHz) δ 188.5 (C1), 159.8 (C3), 159.5 (C12), 135.3 (C5), 129.1 (C10+C14), 127.9 (C4), 127.5 (C9), 126.6 (C2/C6), 126.0 (C2/C6), 114.8 (C4), 114.1 (C11+C13), 70.8 (C8), 55.3 (C15).



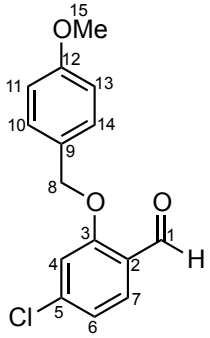
4-Methoxy-2-(4-methoxybenzyloxy)benzaldehyde (2.72e). ALN-3-261. Pale yellow cubes from Hexanes/EtOAc (83%): mp 94-95 °C; ^{1}H NMR (500 MHz) δ 10.32 (s, 1 H), 7.80 (d, *J* = 8.7 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.53 (dd, *J* = 8.7, 2.2 Hz, 1 H), 6.50 (d, *J* = 2.2 Hz, 1 H), 5.05 (s, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz) δ 188.2, 166.0, 162.8, 159.6, 130.3, 129.0, 119.2, 114.0, 106.1, 99.2, 70.2, 55.4, 55.2; IR (CH_2Cl_2) 2937, 1676, 1601, 1259 cm^{-1}; HRMS (CI) *m*/z calculated for $[C_{16}H_{17}O_4]^+$ (M+H), 273.1121; found, 273.1127.

NMR Assignments. ^{1}H NMR (500 MHz) δ 10.32 (s, 1 H, C1-H), 7.80 (d, *J* = 8.7 Hz, 1 H, C7-H), 7.34 (d, *J* = 8.8 Hz, 2 H, C11+C15-H), 6.91 (d, *J* = 8.8 Hz, 2 H, C12+C14-H), 6.53 (dd, *J* = 8.7, 2.2 Hz, 1 H, C6-H), 6.50 (d, *J* = 2.2 Hz, 1 H, C4-H), 5.05 (s, 2 H, C9-H), 3.82 (s, 3 H, C8-H), 3.79 (s, 3 H, C16-H); ^{13}C NMR (125 MHz) δ 188.2 (C1), 166.0 (C5), 162.8 (C3), 159.6 (C13), 130.3 (C7), 129.0 (C11+C15), 127.9 (C10), 119.2 (C2), 114.0 (C12+C14), 106.1 (C6), 99.2 (C4), 70.2 (C9), 55.4 (C8), 55.2 (C16).



2-(4-Methoxybenzyloxy)-4-methylbenzaldehyde (2.72f). ALN-4-27. Colorless needles from EtOAc (71%): mp 113-114 °C; ^{1}H NMR (400 MHz) δ 10.44 (s, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.87-6.84 (comp, 2 H), 5.10 (s, 2 H), 3.83 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.3, 161.2, 159.5, 147.3, 129.0, 128.2, 128.1, 122.9, 121.8, 114.0, 113.5, 70.1, 55.2, 22.2; IR (CH_2Cl_2) 2931, 1681, 1607, 1515, 1250, 816 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{15}O_3]^-$ (M-H), 255.1021; found, 255.1019.

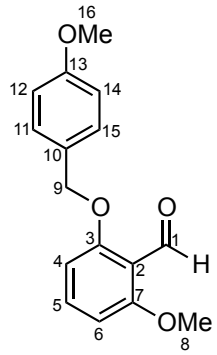
NMR Assignments. ^{1}H NMR (400 MHz) δ 10.44 (s, 1 H, C1-H), 7.75 (d, *J* = 7.6 Hz, 1 H, C7-H), 7.36 (d, *J* = 8.8 Hz, 2 H, C11+C15-H), 6.93 (d, *J* = 8.8 Hz, 2 H, C12+C14-H), 6.87-6.84 (comp, 2 H, C6+C4-H), 5.10 (s, 2 H, C9-H), 3.83 (s, 3 H, C16-H), 2.40 (s, 3 H, C8-H); ^{13}C NMR (100 MHz) δ 189.3 (C1), 161.2 (C3), 159.5 (C13), 147.3 (C5), 129.0 (C11+C15), 128.2 (C7/C10), 128.1 (C7/C10), 122.9 (C2), 121.8 (C6), 114.0 (C12+C14), 113.5 (C4), 70.1 (C9), 55.2 (C16), 22.2 (C8).



4-Chloro-2-(4-methoxybenzyloxy)benzaldehyde (2.72g). ALN-4-271. Colorless cubes from Hexanes (78%): mp 82-83 °C; ^{1}H NMR (400 MHz) δ 10.42 (s, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 7.08 (d, *J* = 1.7 Hz, 1 H), 7.04 (d, *J* = 8.2 Hz, 1 H), 6.94 (d, *J* = 8.9 Hz, 2 H), 5.10 (s, 2 H), 3.84 (s, 3 H); ^{13}C NMR (100 MHz) δ 188.5, 161.3, 159.7, 141.7, 129.4, 129.2, 127.2, 123.6, 121.3, 114.1, 113.6, 70.6,

55.2; IR (CH_2Cl_2) 2837, 1686, 1592, 1240 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{13}O_3Cl]^{+\bullet}$ ($M^{+\bullet}$), 276.0553; found, 276.0550.

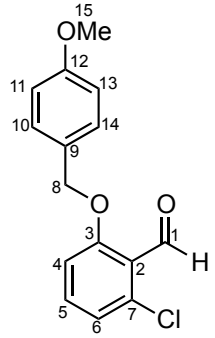
NMR Assignments. ^1H NMR (400 MHz) δ 10.42 (s, 1 H, C1-H), 7.78 (d, *J* = 8.2 Hz, 1 H, C7-H), 7.36 (d, *J* = 8.9 Hz, 2 H, C10+C14-H), 7.08 (d, *J* = 1.7 Hz, 1 H, C4-H), 7.04 (d, *J* = 8.2 Hz, 1 H, C6-H), 6.94 (d, *J* = 8.9 Hz, 2 H, C11+C13-H), 5.10 (s, 2 H, C8-H), 3.84 (s, 3 H, C15-H); ^{13}C NMR (100 MHz) δ 188.5 (C1), 161.3 (C3), 159.7 (C12), 141.7 (C5), 129.4 (C7), 129.2 (C10+C14), 127.2 (C9), 123.6 (C2), 121.3 (C6), 114.1 (C11+C13), 113.6 (C4), 70.6 (C8), 55.2 (C15).



2-Methoxy-6-(4-methoxybenzyloxy)benzaldehyde (2.72h). ALN-4-126. Cream-colored powder from aqueous MeOH (80%): mp 97-98 °C; ^1H NMR (400 MHz) δ 10.55 (s, 1 H), 7.41 (t, *J* = 8.5 Hz, 1 H), 7.36 (d, *J* = 8.9 Hz, 2 H), 6.90 (d, *J* = 8.9 Hz, 2 H), 6.63 (d, *J* = 8.5 Hz, 1 H), 6.57 (d, *J* = 8.5 Hz, 1 H), 5.09 (s, 2 H), 3.89 (s, 3 H), 3.80 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.3, 161.7, 161.6, 159.4, 135.7, 128.7, 128.2, 114.7, 114.0, 105.3, 104.1, 70.5, 56.0, 55.2; IR (CH_2Cl_2) 2934, 1688, 1595, 1474, 1251, 1107 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{17}O_4]^+$ (M+H), 273.1127; found, 273.1126.

NMR Assignments. ^1H NMR (400 MHz) δ 10.55 (s, 1 H, C1-H), 7.41 (t, *J* = 8.5 Hz, 1 H, C5-H), 7.36 (d, *J* = 8.9 Hz, 2 H, C11+C15-H), 6.90 (d, *J* = 8.9 Hz, 2 H, C12+C14-H), 6.63 (d, *J* = 8.5 Hz, 1 H, C4-H), 6.57 (d, *J* = 8.5 Hz, 1 H, C6-H), 5.09 (s, 2

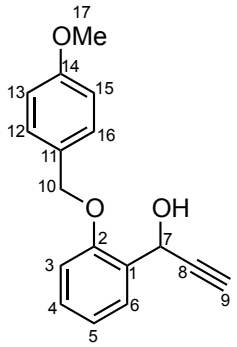
H, C9-H), 3.89 (s, 3 H, C8-H), 3.80 (s, 3 H, C16-H); ^{13}C NMR (100 MHz) δ 189.3 (C1), 161.7 (C3/C7), 161.6 (C3/C7), 159.4 (C13), 135.7 (C5), 128.7 (C11+C15), 128.2 (C10), 114.7 (C2), 114.0 (C12+C14), 105.3 (C4), 104.1 (C6), 70.5 (C9), 56.0 (C8), 55.2 (C16).



6-Chloro-2-(4-methoxybenzyloxy)benzaldehyde (2.72i). ALN-4-284. Colorless powder from Hexanes/EtOAc (89%): mp 98-99 °C; ^{1}H NMR (400 MHz) δ 10.53 (s, 1 H), 7.39-7.34 (comp, 3 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 5.10 (s, 2 H), 3.81 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.1, 161.4, 159.6, 135.8, 134.4, 128.9, 127.6, 123.4, 122.7, 114.1, 111.8, 70.8, 55.3; IR (CH_2Cl_2) 2836, 1695, 1587, 1515, 1249 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{13}O_3Cl]^{+\bullet}$ ($M^{+\bullet}$), 276.0553; found, 276.0553.

NMR Assignments. ^{1}H NMR (400 MHz) δ 10.53 (s, 1 H, C1-H), 7.39-7.34 (comp, 3 H, C10+C14/C5-H), 7.02 (d, *J* = 8.0 Hz, 1 H, C6-H), 6.96 (d, *J* = 8.0 Hz, 1 H, C4-H), 6.92 (d, *J* = 8.5 Hz, 2 H, C11+C13-H), 5.10 (s, 2 H, C8-H), 3.81 (s, 3 H, C15-H); ^{13}C NMR (100 MHz) δ 189.1 (C1), 161.4 (C12), 159.6 (C3), 135.8 (C5), 134.4 (C7), 128.9 (C10+C14), 127.6 (C9), 123.4 (C6), 122.7 (C2), 114.1 (C11+C13), 111.8 (C4), 70.8 (C8), 55.3 (C15).

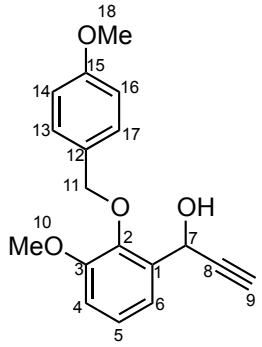
Representative Procedure for Preparation of Propargyl Alcohols 2.73a–i.



1-(2-(4-Methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73a). ALN-3-223. A solution of ethynyl magnesium bromide (24 mL, 12 mmol, 0.5 M in THF) was added to a stirred solution of **2.72a** (2.4 g, 10 mmol) in THF (100 mL) at 0 ˚C. After 3 h at 0 ˚C, saturated aqueous NH_4Cl (50 mL) was added, the ice bath was removed, and the reaction was warmed to room temperature. The aqueous layer was washed with Et_2O (3 x 30 mL), and the combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was purified by passing through a plug of silica gel eluting with Hexanes:EtOAc (1:1) to afford 2.6 g (99%) of **2.73a** as a yellow oil; ^{1}H NMR (500 MHz) δ 7.55 (dd, *J* = 7.3, 1.7 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.29 (dt, *J* = 7.7, 2.0 Hz, 1 H), 7.00-6.97 (comp, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 5.69 (dd, *J* = 6.6, 2.0 Hz, 1 H), 5.08, 5.06 (ABq, *J* = 11.2 Hz, 2 H), 3.80 (s, 3 H), 3.10 (d, *J* = 6.6 Hz, 1 H), 2.60 (d, *J* = 2.2 Hz, 1 H); ^{13}C NMR (125 MHz) δ 159.5, 155.9, 129.7, 129.1, 128.6, 128.4, 128.3, 127.9, 121.1, 114.1, 112.3, 83.2, 74.0, 70.1, 61.3, 55.3; IR (CH_2Cl_2) 3434, 2936, 2112, 1515, 1029 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{16}O_3]^{+\bullet}$ ($M^{+\bullet}$), 268.1099; found, 268.1099.

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.55 (dd, *J* = 7.3, 1.7 Hz, 1 H, C6-H), 7.36 (d, *J* = 8.8 Hz, 2 H, C12+C16-H), 7.29 (dt, *J* = 7.7, 2.0 Hz, 1 H, C4-H), 7.00-6.97 (comp, 2 H, C3/C5-H), 6.91 (d, *J* = 8.8 Hz, 2 H, C13+C15-H), 5.69 (dd, *J* = 6.6, 2.0 Hz, 1 H, C7-H), 5.08, 5.06 (ABq, *J* = 11.2 Hz, 2 H, C10-H), 3.80 (s, 3 H, C17-H), 3.10 (d, *J*

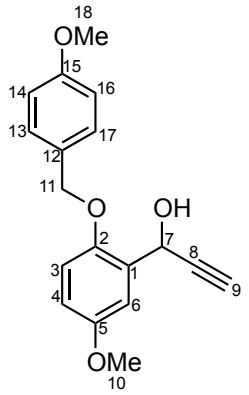
= 6.6 Hz, 1 H, C7-OH), 2.60 (d, *J* = 2.2 Hz, 1 H, C9-H); ^{13}C NMR (125 MHz) δ 159.5 (C14), 155.9 (C2), 129.7 (C4), 129.1 (C12+C16), 128.6 (C11/C1), 128.4 (C11/C1), 127.9 (C6), 121.1 (C5), 114.1, C13+C15), 112.3 (C3), 83.2 (C8), 74.0 (C9), 70.1 (C10), 61.3 (C7), 55.3 (C17).



1-(3-Methoxy-2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73b). ALN-3-285. Colorless solid from Hexanes/EtOAc (92%): mp 88-89 °C; ^{1}H NMR (400 MHz) δ 7.42 (d, *J* = 8.0 Hz, 2 H), 7.16 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 5.58 (dd, *J* = 8.0, 2.4 Hz, 1 H), 5.11, 5.09 (ABq, *J* = 11.2 Hz, 2 H), 3.91 (s, 3 H), 3.82 (s, 3 H), 2.95 (d, *J* = 6.8 Hz, 1 H), 2.61 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (100 MHz) δ 159.6, 152.6, 145.1, 134.4, 130.2, 129.4, 124.3, 119.5, 113.9, 112.8, 83.8, 74.6, 74.1, 60.8, 55.9, 55.2; IR (CH_2Cl_2) 3436, 3285, 2938, 2359, 1514, 1479, 1250, 791 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{18}O_4]^{+\bullet}$ ($M^{+\bullet}$), 298.1200; found, 298.1208.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.42 (d, *J* = 8.4 Hz, 2 H, C13+17-H), 7.16 (dd, *J* = 7.6, 1.6 Hz, 1 H, C4-H), 7.09 (t, *J* = 7.6 Hz, 1 H, C5-H), 6.95 (dd, *J* = 8.4, 1.6 Hz, 1 H, C6-H), 6.92 (d, *J* = 8.4 Hz, 2 H, C14+C16-H), 5.58 (dd, *J* = 8.0, 2.4 Hz, 1 H, C7-H), 5.11, 5.09 (ABq, *J* = 11.2 Hz, 2 H, C11-H), 3.91 (s, 3 H, C10-H), 3.82 (s, 3 H, C18-H), 2.95 (d, *J* = 6.8 Hz, 1 H, C7-OH), 2.61 (d, *J* = 2.0 Hz, 1 H, C9-H); ^{13}C NMR

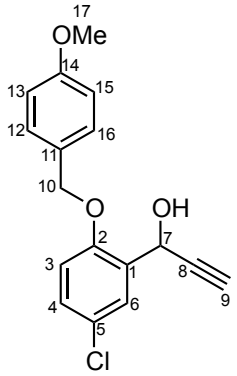
(100 MHz) δ 159.6 (C15), 152.6 (C2), 145.1 (C3), 134.4 (C1), 130.2 (C13+C17), 129.4 (C12), 124.3 (C5), 119.5 (C6), 113.9 (C14+C16), 112.8 (C4), 83.8 (C8), 74.6 (C9), 74.1 (C11), 60.8 (C7), 55.9 (C10), 55.2 (C18).



1-(5-Methoxy-2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73c). ALN-4-30. Purified by silica gel plug filtration eluting with Hexanes:EtOAc (1:1) to afford a yellow oil (99%); ^{1}H NMR (400 MHz) δ 7.36 (d, *J* = 8.6 Hz, 2 H), 7.15 (d, *J* = 3.1 Hz, 1 H), 6.93-6.91 (comp, 3 H), 6.82 (dd, *J* = 8.9, 3.1 Hz, 1 H), 5.66 (s, 1 H), 5.04, 5.02 (ABq, *J* = 10.9 Hz, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.10 (1 H), 2.62 (s, 1 H); ^{13}C NMR (100 MHz) δ 159.4, 153.8, 149.8, 129.8, 129.0, 128.7, 114.1, 113.9, 113.8, 113.6, 83.1, 74.1, 70.9, 60.9, 55.6, 55.1; IR (CH_2Cl_2) 3443, 3285, 2937, 1613, 1515, 1247, 1034 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{18}O_4]^{+\bullet}$ ($M^{+\bullet}$), 298.1205; found, 298.1207.

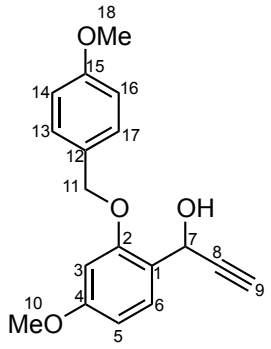
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.36 (d, *J* = 8.6 Hz, 2 H, C13+C17-H), 7.15 (d, *J* = 3.1 Hz, 1 H, C3-H), 6.93-6.91 (comp, 3 H, C14+C16-H/C6-H), 6.82 (dd, *J* = 8.9, 3.1 Hz, 1 H, C4-H), 5.66 (s, 1 H, C7-H), 5.04, 5.02 (ABq, *J* = 10.9 Hz, 2 H, C11-H), 3.82 (s, 3 H, C18-H), 3.79 (s, 3 H, C10-H), 3.10 (1 H, C7-OH), 2.62 (s, 1 H, C9-H); ^{13}C NMR (100 MHz) δ 159.4 (C15), 153.8 (C5), 149.8 (C2), 129.8 (C12), 129.0

(C13+C17), 128.7 (C1), 114.1 (C4), 113.9 (C14+C16), 113.8 (C3/C6), 113.6 (C3/C6), 83.1 (C8), 74.1 (C9), 70.9 (C11), 60.9 (C7), 55.6 (C10), 55.1 (C18).



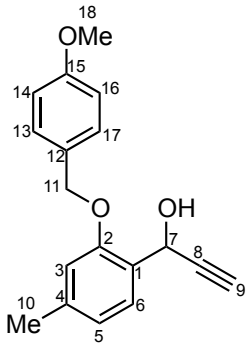
1-(5-Chloro-2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73d). ALN-3-283. Colorless cubes from Hexanes/EtOAc (94%): mp 86-87 °C; ^{1}H NMR (400 MHz) δ 7.59 (d, *J* = 2.7 Hz, 1 H), 7.36 (d, *J* = 8.6 Hz, 2 H), 7.25 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.7 Hz, 1 H), 5.69 (dd, *J* = 6.1, 2.2 Hz, 1 H), 5.04 (s, 2 H), 3.82 (s, 3 H), 3.22 (d, *J* = 6.1 Hz, 1 H), 2.64 (d, *J* = 2.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 159.4, 154.2, 130.2, 129.1, 129.0, 127.9, 127.7, 125.9, 114.0, 113.5, 82.5, 74.4, 70.4, 60.0, 55.1; IR (CH_2Cl_2) 3417 3292, 2935, 2118, 1515, 1245 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{14}O_3Cl]^-$ (M-H), 301.0631; found, 301.0628.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.59 (d, *J* = 2.7 Hz, 1 H, C6-H), 7.36 (d, *J* = 8.6 Hz, 2 H, C12+C16-H), 7.25 (dd, *J* = 8.7, 2.7 Hz, 1 H, C4-H), 6.93 (d, *J* = 8.6 Hz, 2 H, C13+C15-H), 6.89 (d, *J* = 8.7 Hz, 1 H, C3-H), 5.69 (dd, *J* = 6.1, 2.2 Hz, 1 H, C7-H), 5.04 (s, 2 H, C10-H), 3.82 (s, 3 H, C17-H), 3.22 (d, *J* = 6.1 Hz, 1 H, C7-OH), 2.64 (d, *J* = 2.2 Hz, 1 H, C9-H); ^{13}C NMR (100 MHz) δ 159.4 (C14), 154.2 (C2), 130.2 (C11), 129.1 (C6), 129.0 (C12+C16), 127.9 (C1), 127.7 (C4), 125.9 (C5), 114.0 (C13+C15), 113.5 (C3), 82.5 (C8), 74.4 (C9), 70.4 (C10), 60.0 (C7), 55.1 (C17).



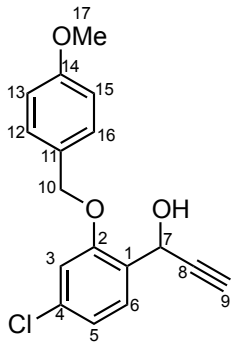
1-(4-Methoxy-2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73e). ALN-3-263. Yellow needles from Hexanes/EtOAc (99%): mp 64-65 °C; ^{1}H NMR (400 MHz) δ 7.49 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 6.55 (d, *J* = 2.3 Hz, 1 H), 6.51 (dd, *J* = 8.4, 2.3 Hz, 1 H), 5.66 (dd, *J* = 6.5, 2.3 Hz, 1 H), 5.04, 5.02 (ABq, *J* = 11.2 Hz, 2 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.02 (d, *J* = 6.3 Hz, 1 H), 2.61 (d, *J* = 2.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 160.9, 159.4, 156.9, 129.0, 128.6, 128.3, 121.4, 114.0, 104.5, 100.1, 83.4, 73.7, 70.1, 60.5, 55.3, 55.2; IR (CH_2Cl_2) 3285, 2937, 2360, 1612, 1515, 1250, 826 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{18}O_4]^{+\bullet}$ ($M^{+\bullet}$), 298.1205; found, 298.1202.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.49 (d, *J* = 8.4 Hz, 1 H, C6-H), 7.37 (d, *J* = 8.0 Hz, 2 H, C13+C17-H), 6.92 (d, *J* = 8.0 Hz, 2 H, C14+C16-H), 6.55 (d, *J* = 2.3 Hz, 1 H, C3-H), 6.51 (dd, *J* = 8.4, 2.3 Hz, 1 H, C6-H), 5.66 (dd, *J* = 6.5, 2.3 Hz, 1 H, C7-H), 5.04, 5.02 (ABq, *J* = 11.2 Hz, 2 H, C11-H), 3.81 (s, 3 H, C18-H), 3.79 (s, 3 H, C10-H), 3.02 (d, *J* = 6.3 Hz, 1 H, C7-OH), 2.61 (d, *J* = 2.2 Hz, 1 H, C9-H); ^{13}C NMR (100 MHz) δ 160.9 (C4), 159.4 (C15), 156.9 (C2), 129.0 (C13+C17), 128.6 (C6), 128.3 (C12), 121.4 (C1), 114.0 (C14+C16), 104.5 (C5), 100.1 (C3), 83.4 (C8), 73.7, (C9) 70.1 (C11), 60.5 (C7), 55.3 (C10), 55.2 (C18).



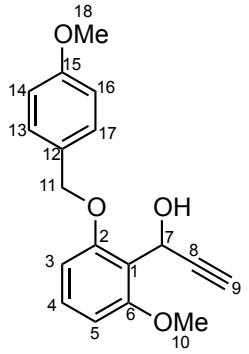
1-(2-(4-Methoxybenzyloxy)-4-methylphenyl)prop-2-yn-1-ol (2.73f). ALN-3-300. Colorless cubes from Hexanes/EtOAc (99%): mp 63-64 °C; ^{1}H NMR (400 MHz) δ 7.45 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 8.6 Hz, 2 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 6.84-6.82 (comp, 2 H), 5.68 (dd, *J* = 6.6, 2.3 Hz, 1 H), 5.07, 5.05 (ABq, *J* = 11.1 Hz, 2 H), 3.82 (s, 3 H), 3.17 (d, *J* = 6.5 Hz, 1 H), 2.61 (d, *J* = 2.3 Hz, 1 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz) δ 159.4, 155.8, 139.8, 129.0, 128.5, 127.6, 125.8, 121.6, 113.9, 113.1, 83.4, 73.7, 70.0, 60.9, 55.2, 21.5; IR (CH_2Cl_2) 3433, 3286, 2934, 2115, 1613, 1515, 1024, 821 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{17}O_3]^-$ (M-H), 281.1176; found, 281.1178.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.45 (d, *J* = 8.0 Hz, 1 H, C6-H), 7.39 (d, *J* = 8.6 Hz, 2 H, C13+C17-H), 6.93 (d, *J* = 8.6 Hz, 2 H, C14+C16-H), 6.84-6.82 (comp, 2 H, C5+C6-H), 5.68 (dd, *J* = 6.6, 2.3 Hz, 1 H, C7-H), 5.07, 5.05 (ABq, *J* = 11.1 Hz, 2 H, C11-H), 3.82 (s, 3 H, C18-H), 3.17 (d, *J* = 6.5 Hz, 1 H, C7-OH), 2.61 (d, *J* = 2.3 Hz, 1 H, C9-H), 2.37 (s, 3 H, C10-H); ^{13}C NMR (100 MHz) δ 159.4 (C15), 155.8 (C2), 139.8 (C4), 129.0 (C13+C17), 128.5 (C12), 127.6 (C6), 125.8 (C1), 121.6 (C5), 113.9 (C14+C16), 113.1 (C3), 83.4 (C8), 73.7 (C9), 70.0 (C11), 60.9 (C8), 55.2 (C18), 21.5 (C10).



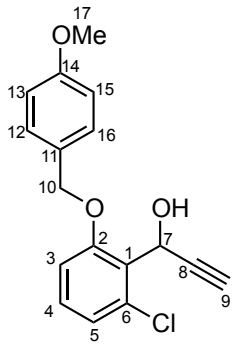
1-(4-Chloro-2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73g). ALN-4-272. Purified by silica gel plug filtration eluting with Hexanes:EtOAc (1:1) to afford a colorless oil (99%); ^{1}H NMR (400 MHz) δ 7.50 (d, *J* = 8.6 Hz, 1 H), 7.36 (d, *J* = 8.6 Hz, 2 H), 7.00-6.97 (comp, 2 H), 6.93 (d, *J* = 8.6 Hz, 2 H), 5.65 (s, 1 H), 5.01 (s, 2 H), 3.83 (s, 3 H), 3.18 (s, 1 H), 2.60 (s, 1 H); ^{13}C NMR (100 MHz) δ 159.5, 156.2, 134.9, 129.1, 128.6, 127.7, 127.2, 120.9, 114.0, 112.8, 82.8, 74.2, 70.3, 60.0, 55.1; IR (CH_2Cl_2) 3431, 3297, 2936, 2252, 1596, 1515, 1245 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{17}H_{14}O_3Cl]^+$ (M+H), 325.0602; found, 325.0603.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.50 (d, *J* = 8.6 Hz, 1 H, C5-H), 7.36 (d, *J* = 8.6 Hz, 2 H, C12+C16-H), 7.00-6.97 (comp, 2 H, C3/C6-H), 6.93 (d, *J* = 8.6 H, 2 H, C13+C15-H), 5.65 (s, 1 H, C7-H), 5.01 (s, 2 H, C10-H), 3.81 (s, 3 H, C17-H), 3.18 (s, 1 H, C7-OH), 2.60 (s, 1 H, C9-H); ^{13}C NMR (100 MHz) δ 159.5 (C14), 156.2 (C2), 134.9 (C4), 129.1 (C12+C16), 128.6 (C11), 127.7 (C5), 127.2 (C1), 120.9 (C6), 114.0 (C13+C15-H), 112.8 (C3), 82.8 (C8), 74.2 (C9), 70.3 (C10), 60.0 (C7), 55.1 (C17).



1-(2-Methoxy-6-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73h). ALN-4-153. Colorless powder from Hexanes/EtOAc (87%): mp 117-118 °C; ^{1}H NMR (400 MHz) δ 7.39 (d, *J* = 8.6 Hz, 2 H), 7.21 (t, *J* = 8.4 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 5.98 (dd, *J* = 11.5, 2.2 Hz, 1 H), 5.08 (s, 2 H), 4.13 (d, *J* = 11.7 Hz, 1 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 2.45 (s, 1 H); ^{13}C NMR (100 MHz) δ 159.5, 157.3, 156.6, 129.5, 129.0, 128.4, 117.3, 114.0, 105.9, 104.6, 84.8, 71.2, 70.5, 56.4, 56.0, 55.2; IR (CH_2Cl_2) 3536, 3285, 2937, 1596, 1476, 1097 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{18}O_4]^{+\bullet}$ ($M^{+\bullet}$), 298.1205; found, 298.1202.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.39 (d, *J* = 8.6 Hz, 2 H, C13+C17-H), 7.21 (t, *J* = 8.4 Hz, 1 H, C4-H), 6.92 (d, *J* = 8.6 Hz, 2 H, C14+C16-H), 6.65 (d, *J* = 8.0 Hz, 1 H, C3-H), 6.60 (d, *J* = 8.4 Hz, 1 H, C5-H), 5.98 (dd, *J* = 11.5, 2.2 Hz, 1 H, C7-H), 5.08 (s, 2 H, C11-H), 4.13 (d, *J* = 11.7 Hz, 1 H, C7-OH), 3.88 (s, 3 H, C10-H), 3.82 (s, 3 H, C18-H), 2.45 (s, 1 H, C9-H); ^{13}C NMR (100 MHz) δ 159.5 (C15), 157.3 (C2), 156.6 (C6), 129.5 (C4), 129.0 (C13+C17), 128.4 (C12), 117.3 (C1), 114.0 (C14+C16), 105.9 (C3), 104.6 (C5), 84.8 (C8), 71.2 (C11), 70.5 (C9), 56.4 (C7), 56.0 (C10), 55.2 (C18).

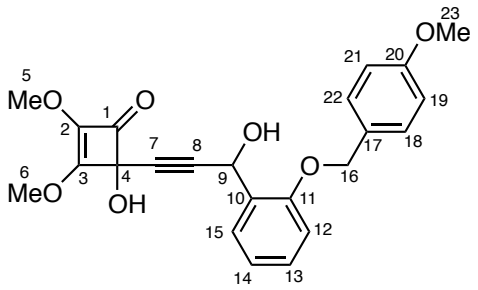


1-(6-Chloro-2-(4-methoxybenzyloxy)phenyl)prop-2-yn-1-ol (2.73i). ALN-4-285. Colorless needles from Hexanes/EtOAc (98%): 92-93 °C; ^{1}H NMR (400 MHz) δ 7.41 (d, *J* = 8.9 Hz, 2 H), 7.19 (t, *J* = 8.2 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 1 H), 6.94-6.92 (comp, 3 H), 5.98 (app d, *J* = 8.2 Hz, 1 H), 5.12, 5.11 (ABq, *J* = 11.3 Hz, 2 H), 4.06 (app d, *J* = 10.6 Hz, 1 H), 3.83 (s, 3 H), 2.52 (s, 1 H); ^{13}C NMR (100 MHz) δ 159.7, 157.5, 132.9, 129.6, 129.3, 127.6, 126.9, 122.6, 114.2, 111.5, 83.3, 72.5, 71.0, 59.9, 55.3; IR (CH_2Cl_2) 3536, 3290, 2936, 1515, 1250, 1030 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{15}O_3Cl]^{+\bullet}$ ($M^{+\bullet}$), 302.0710; found, 302.0711.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.41 (d, *J* = 8.9 Hz, 2 H, C12+C16-H), 7.19 (t, *J* = 8.2 Hz, 1 H, C4-H), 7.01 (d, *J* = 8.2 Hz, 1 H, C5-H), 6.94-6.92 (comp, 3 H, C13+C15/C5-H), 5.98 (app d, *J* = 8.2 Hz, 1 H, C7-H), 5.12, 5.11 (ABq, *J* = 11.3 Hz, 2 H, C10-H), 4.06 (app d, *J* = 10.6 Hz, 1 H, C7-OH), 3.83 (s, 3 H, C17-H), 2.52 (s, 1 H, C9-H); ^{13}C NMR (100 MHz) δ 159.7 (C14), 157.5 (C2), 132.9 (C6), 129.6 (C11), 129.3 (C12+C16), 127.6 (C1), 126.9 (C3), 122.6 (C5), 114.2 (C13+C15), 111.5 (C4), 83.3 (C8), 72.5 (C9), 71.0 (C10), 59.9 (C17), 55.3 (C7).

Representative Procedure for Preparation of Quinones 2.74a–i.

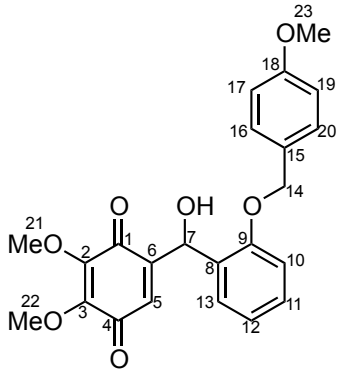
Note: The squarate **2.9** and **2.73a-i** were separately dried *via* azeotropic removal of H_2O from PhH 2x before subjecting to the dianion reaction.



4-Hydroxy-4-(3-hydroxy-3-(2-(4-methoxybenzyloxy)phenyl)prop-1-ynyl)-2,3-dimethoxycyclobut-2-enone (2.74a). ALN-3-293. A solution of *n*-BuLi (3.5 mL, 8.2 mmol, 2.37 M in Hexanes) was added to a stirred solution of **2.73a** (1.0 g, 3.7 mmol) in THF (25 mL) at 0 ˚C. The solution was stirred for 4 min at which time a solution of **2.9** (0.69 g, 4.8 mmol) in THF (10 mL) was transferred *via* cannula to the dianion. The solution was stirred at 0 ˚C for 1.5 h, whereupon saturated aqueous NH_4Cl (30 mL) was added, and the reaction was warmed to room temperature over 10 min. The aqueous layer was diluted with H_2O (20 mL), and then washed with Et_2O (3 x 30 mL). The combined organic layers were washed with H_2O (1 x 20 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was rapidly purified by flash column chromatography eluting with Hexanes:EtOAc (2:1) to afford 0.79 g (54%) of **2.74a** as a red oil as a mixture of diastereomers; ^{1}H NMR (500 MHz, C_6D_6) δ 7.80-7.56 (m, 1 H), 7.27-7.25 (comp, 2 H), 7.04-6.99 (m, 1 H), 6.87-6.82 (comp, 3 H), 6.62 (s, 0.5 H), 6.61 (s, 0.5 H), 6.03 (br s, 1 H), 5.20 (s, 0.5 H), 5.13 (s, 0.5 H), 4.73-4.68 (comp, 2 H), 4.27 (br s, 0.5 H), 4.21 (s, 0.5 H), 3.64 (s, 1.5 H), 3.62 (s, 1.5 H), 3.45 (s, 1.5 H), 3.44 (s, 1.5 H), 3.36 (s, 1.5 H), 3.35 (s, 1.5 H); ^{13}C NMR (125 MHz, C_6D_6) δ 181.7, 181.6, 165.6, 165.5, 159.9, 156.1 x 2, 135.7, 129.5 x 2, 129.2 x 2, 128.3, 128.2, 121.4, 121.3, 114.4, 112.6, 112.5, 90.2, 90.1, 80.4, 80.3, 79.1, 79.0, 60.8, 60.6,

59.6 x 2, 58.1, 54.9; IR (CH_2Cl_2) 3368, 2953, 1778, 1632, 1470, 1345, 1244, 1038 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{23}H_{22}O_7]^{+\bullet}$ ($M^{+\bullet}$), 410.1366; found, 410.1370.

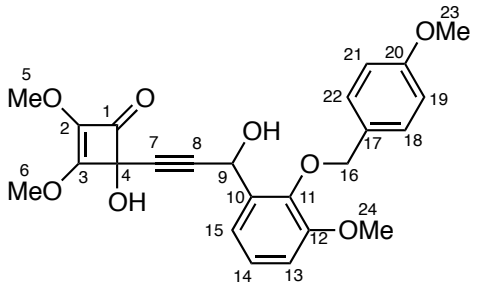
NMR Assignments. ^1H NMR (500 MHz, C_6D_6) δ 7.80-7.56 (m, 1 H, C15-H), 7.27-7.25 (comp, 2 H, C22+C18-H), 7.04-6.99 (m, 1 H, C13-H), 6.87-6.82 (comp, 3 H, C19+C21/C14-H), 6.62 (s, 0.5 H, C12-H), 6.61 (s, 0.5 H, C12-H), 6.03 (br s, 1 H, C9-H), 5.20 (s, 0.5 H, C4-OH), 5.13 (s, 0.5 H, C4-OH), 4.73-4.68 (comp, 2 H, C16-H), 4.27 (br s, 0.5 H, C9-OH), 4.21 (s, 0.5 H, C9-OH), 3.64 (s, 1.5 H, C6-H), 3.62 (s, 1.5 H, C6-H), 3.45 (s, 1.5 H, C5-H), 3.44 (s, 1.5 H, C5-H), 3.36 (s, 1.5 H, C23-H), 3.35 (s, 1.5 H, C23-H); ^{13}C NMR (125 MHz, C_6D_6) δ 181.7 (C1), 181.6 (C1), 165.6 (C3), 165.5 (C3), 159.9 (C20), 156.1 x 2 (C11), 135.7 (C2), 129.5 x 2 (C10+C13), 129.2 x 2 (C22+C18), 128.3 (C15), 128.2 (C15), 121.4 (C14), 121.3 (C14), 114.4 (C19+C21), 112.6 (C12), 112.5 (C12), 90.2 (C4), 90.1 (C4), 80.4 (C7), 80.3 (C7), 79.1 (C8), 79.0 (C8), 70.1 x 2 (C16), 60.8 (C9), 60.6 (C9), 59.6 x 2 (C6), 58.1 (C5), 54.9 (C23).



5-(Hydroxy(2-(4-methoxybenzyloxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75a). ALN-3-293. The diol **2.74a** (0.79 g, 1.9 mmol) was dissolved in $PhCH_3$ (19 mL), sparged with argon for 15 min, placed in an oil bath (~130 °C), and heated under reflux for 4 h. It is important to note that these reactions need to stay under Ar atmosphere. Brief exposure of the reaction to atmosphere results in lower

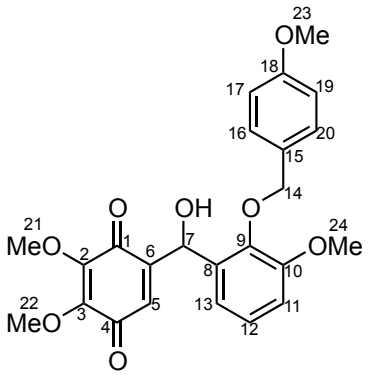
yields. The reaction was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford 0.65 g (78%) of **2.75a** as a red oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.37 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.28-7.23 (comp, 3 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.3 (d, *J* = 1.3 Hz, 1 H), 6.06 (s, 1 H), 4.97, 4.95 (ABq, *J* = 11.2 Hz, 2 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.8, 184.5, 161.0, 156.9, 150.2, 146.3, 146.0, 130.9, 130.7, 130.4, 130.3, 130.2, 128.7, 121.8, 114.9, 113.6, 71.2, 65.0, 61.7, 61.6, 55.7; IR (CH_2Cl_2) 3487, 2950, 1656, 1603, 1515, 1245, 755 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{23}H_{23}O_7]^+$ (M+H), 411.1444; found, 411.1450.

NMR Assignments. ^{1}H NMR (500 MHz, CD_3OD) δ 7.37 (dd, *J* = 7.6, 1.7 Hz, 1 H, C13-H), 7.28-7.23 (comp, 3 H, C16+C20/C11-H), 7.02 (d, *J* = 8.0 Hz, 1 H, C10-H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1 H, C12-H), 6.84 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.3 (d, *J* = 1.3 Hz, 1 H, C5-H), 6.06 (s, 1 H, C7-H), 4.97, 4.95 (ABq, *J* = 11.2 Hz, 2 H, C14-H), 3.91 (s, 3 H, C22-H), 3.83 (s, 3 H, C21-H), 3.76 (s, 3 H, C23-H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.8 (C4), 184.5 (C1), 161.0 (C18), 156.9 (C9), 150.2 (C6), 146.3 (C2), 146.0 (C3), 130.9 (C8), 130.7 (C5), 130.4 (C16+C20), 130.3 (C15), 130.2 (C11), 128.7 (C13), 121.8 (C12), 114.9 (C17+C19), 113.6 (C10), 71.2 (C14), 65.0 (C7), 61.7 (C21), 61.6 (C22), 55.7 (C23).



4-Hydroxy-4-(3-hydroxy-3-(3-methoxy-2-(4-methoxybenzyloxy)phenyl)prop-1-ynyl)-2,3-dimethoxycyclobut-2-enone (2.74b). ALN-3-286. Purified by flash column chromatography eluting with Hexanes:EtOAc (3:1 to 1:1) to afford **2.74b** as a yellow oil (52%) as a mixture of diastereomers; ^{1}H NMR (600 MHz) δ 7.41-7.39 (m, 1 H), 7.09-7.07 (comp, 2 H), 6.95-6.93 (m, 1 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 5.62-5.60 (m, 1 H), 5.10-5.08 (comp, 2 H), 4.12 (s, 1.5 H), 4.11 (s, 1.5 H), 3.93 (s, 1.5 H), 3.92 (s, 1.5 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.37 (br s, 0.5 H), 3.32 (s, 0.5 H), 3.10 (br s, 1 H); ^{13}C NMR (150 MHz) δ 180.0, 164.2 x 2, 159.6 x 2, 152.7 x 2, 145.2, 145.1, 135.7, 134.1, 130.2, 130.1, 129.5 x 2, 124.4, 119.7 x 2, 114.0, 113.0 x 2, 89.4 x 2, 79.9 x 2, 78.6, 74.7 x 2, 61.1 x 2, 60.1 x 2, 58.6 x 2, 55.9, 55.3; IR (CH_2Cl_2) 3392, 2955, 2839, 1778, 1630, 1514, 1471, 1345, 1251, 1038 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{24}H_{25}O_8]^+$ (M+H), 441.1549; found, 441.1541.

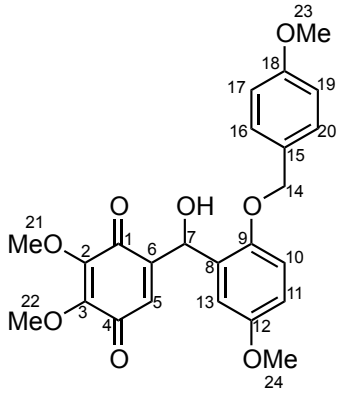
NMR Assignments. ^{1}H NMR (600 MHz) δ 7.41-7.39 (m, 1 H, C18+C22-H), 7.09-7.07 (comp, 2 H, C13+C14-H), 6.95-6.93 (m, 1 H, C15-H), 6.91 (d, *J* = 8.6 Hz, 2 H, C19+C21-H), 5.62-5.60 (m, 1 H, C9-H), 5.10-5.08 (comp, 2 H, C16-H), 4.12 (s, 1.5 H, C6-H), 4.11 (s, 1.5 H, C6-H), 3.93 (s, 1.5 H, C5-H), 3.92 (s, 1.5 H, C5-H), 3.91 (s, 3 H, C24-H), 3.81 (s, 3 H, C23-H), 3.37 (br s, 0.5 H, C4-OH), 3.32 (s, 0.5 H, C4-OH), 3.10 (br s, 1 H, C9-OH); ^{13}C NMR (150 MHz) δ 180.0 (C1), 164.2 x 2 (C3), 159.6 x 2 (C20), 152.7 x 2 (C12), 145.2 (C11), 145.1 (C2), 135.7 (C10), 134.1 (C18+C22), 130.2 (C17), 130.1 (C17), 129.5 x 2 (C17), 124.4 (C14), 119.7 x 2 (C15), 114.0 (C19+C21), 113.0 x 2 (C13), 89.4 x 2 (C8), 79.9 x 2 (C7), 78.6 (C4), 74.7 x 2 (C16), 61.1 x 2 (C9), 60.1 x 2 (C6), 58.6 x 2 (C5), 55.9 (C24), 55.3 (C23).



5-(Hydroxy(3-methoxy-2-(4-methoxybenzyloxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75b). ALN-3-292. Thermolysis of **2.74b** required 3 h. Flash column chromatography eluting with Hexanes:EtOAc (3:1 to 2:1) to afford **2.75b** (66%) as a red oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (d, *J* = 8.7 Hz, 2 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.01 (dd, *J* = 8.2, 1.5 Hz, 1 H), 6.91 (dd, *J* = 8.2, 1.5 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 6.32 (s, 1 H), 6.05 (s, 1 H), 5.01, 4.98 (ABq, *J* = 10.6 Hz, 2 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.8, 184.7, 161.0, 154.3, 150.0, 146.4, 146.2 x 2, 136.2, 131.3, 131.2, 130.7, 125.3, 120.8, 114.8, 113.7, 75.5, 64.9, 61.7, 61.6, 56.4, 55.6; IR (CH_2Cl_2) 3439, 2938, 1656, 1603, 1219 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{24}H_{25}O_8]^+$ (M+H), 441.1549; found, 441.1543.

NMR Assignments. ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (d, *J* = 8.7 Hz, 2 H, C16+C20-H), 7.08 (t, *J* = 8.0 Hz, 1 H, C12-H), 7.01 (dd, *J* = 8.2, 1.5 Hz, 1 H, C11-H), 6.91 (dd, *J* = 8.2, 1.5 Hz, 1 H, C13-H), 6.83 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.32 (s, 1 H, C5-H), 6.05 (s, 1 H, C7-H), 5.01, 4.98 (ABq, *J* = 10.6 Hz, 2 H, C14-H), 3.93 (s, 3 H, C21-H), 3.90 (s, 3 H, C24-H), 3.86 (s, 3 H, C22-H), 3.77 (s, 3 H, C23-H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.8 (C4), 184.7 (C1), 161.0 (C18), 154.3 (C10), 150.0 (C6), 146.4 (C3), 146.2 x 2 (C2+C8), 136.2 (C9), 131.3 (C16+C20), 131.2 (C15), 130.7 (C5), 125.3

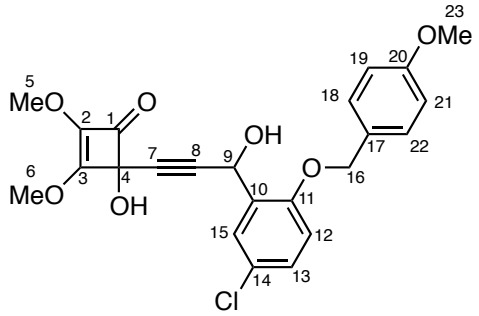
(C12), 120.8 (C13), 114.8 (C17+C19), 113.7 (C11), 75.5 (C14), 64.9 (C7), 61.7 (C22), 61.6 (C21), 56.4 (C24), 55.6 (C23).



5-(Hydroxy(5-methoxy-2-(4-methoxybenzyloxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75c). ALN-4-146. Yield of **2.74c**: 62%. Thermolysis required 2 h. Flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford **2.75c** (72%) as a red oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (d, *J* = 8.7 Hz, 2 H), 6.99 (d, *J* = 3.1 Hz, 1 H), 6.98 (d, *J* = 8.9 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.82 (dd, *J* = 8.9, 3.1 Hz, 1 H), 6.24 (d, *J* = 1.3 Hz, 1 H), 6.02 (s, 1 H), 4.94, 4.90 (ABq, *J* = 11.1 Hz, 2 H), 3.94 (s, 3 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (125 Hz, CD_3OD) δ 185.9, 184.5, 160.9, 155.4, 150.9, 150.0, 146.4, 146.1, 132.3, 130.7, 130.6, 130.4, 115.1, 114.9 x 2, 114.3, 72.0, 64.9, 61.7, 61.6, 56.1, 55.7; IR (CH_2Cl_2) 3487, 2950, 1656, 1603, 1515, 1212, 1033 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{24}H_{24}O_8]^{+\bullet}$ ($M^{+\bullet}$), 440.1471; found, 440.1469.

NMR Assignments. ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (d, *J* = 8.7 Hz, 2 H, C16+C20-H), 6.99 (d, *J* = 3.1 Hz, 1 H, C13-H), 6.98 (d, *J* = 8.9 Hz, 1 H, C10-H), 6.84 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.82 (dd, *J* = 8.9, 3.1 Hz, 1 H, C11-H), 6.24 (d, *J* = 1.3 Hz, 1 H, C5-H), 6.02 (s, 1 H, C7-H), 4.94, 4.90 (ABq, *J* = 11.1 Hz, 2 H, C14-H), 3.94 (s, 3 H,

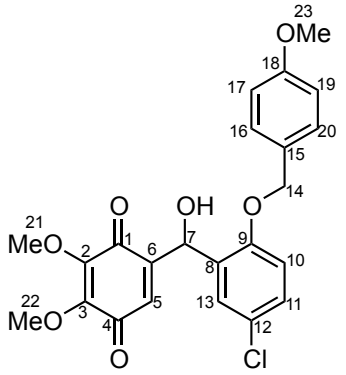
C22-H), 3.86 (s, 3 H, C21-H), 3.78 (s, 3 H, C23-H), 3.75 (s, 3 H, C24-H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.9 (C4), 184.5 (C1), 160.9 (C18), 155.4 (C12), 150.9 (C9), 150.0 (C6), 146.4 (C2), 146.1 (C3), 132.3 (C8), 130.7 (C5), 130.6 (C15), 130.4 (C16+C20), 115.1 (C11), 114.9 (C17+C19+C13), 114.3 (C10), 72.0 (C14), 64.9 (C7), 61.7 (C21), 61.6 (C22), 56.1 (C23), 55.7 (C24).



4-(3-(5-Chloro-2-(4-methoxybenzyloxy)phenyl)-3-hydroxyprop-1-ynyl)-4-hydroxy-2,3-dimethoxycyclobut-2-enone (2.74d). ALN-4-180. Purified by flash column chromatography eluting with CH_2Cl_2:MeOH (100:1) to afford **2.73d** as a yellow oil (64%) as a mixture of diastereomers; major diastereomer: ^{1}H NMR (400 MHz) δ 7.48 (d, *J* = 2.5 Hz, 1 H), 7.33 (d, *J* = 8.9 Hz, 2 H), 7.21 (d, *J* = 2.9 Hz, 1 H), 6.91 (d, *J* = 8.9 Hz, 2 H), 6.88 (m, 1 H), 5.68 (d, *J* = 6.5 Hz, 1 H), 5.03 (s, 2 H), 4.13 (s, 3 H), 3.94 (s, 3 H), 3.86 (s, 1 H), 3.81 (s, 3 H), 3.45 (d, *J* = 6.5 Hz, 1 H); minor diastereomer: ^{1}H NMR (400 MHz) δ 7.46 (d, *J* = 2.4 Hz, 1 H), 7.34 (d *J* = 8.9 Hz, 2 H), 7.23 (d, *J* = 2.4 Hz, 1 H), 6.91 (d, *J* = 8.9 Hz, 2 H), 6.86 (m, 1 H), 5.68 (d, *J* = 6.5 Hz, 1 H), 5.03 (s, 2 H), 4.13 (s, 3 H), 3.94 (s, 3 H), 3.73 (s, 1 H), 3.41 (d, *J* = 6.2 Hz, 1 H); ^{13}C NMR (150 MHz) δ 180.5, 180.4, 164.5, 164.4, 159.6 x 2, 154.3 x 2, 135.6 x 2, 130.1, x 2, 129.2 x 2, 129.1, 129.0, 128.1, 127.8 x 2, 126.0 x 2, 114.1, 113.6 x 2, 88.5 x 2, 80.0, x 2, 78.4 x 2, 70.6, 70.5,

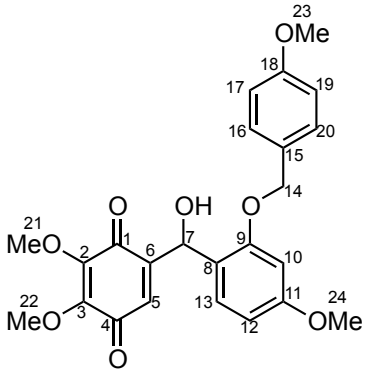
60.4, 60.3, 60.1, 58.6, 55.3 x 2; IR (CH_2Cl_2) 3370, 2954, 1778, 1629, 1345, 1037 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{23}H_{22}O_7Cl]^+$ (M+H), 445.1054; found, 445.1060.

NMR Assignments. Major diastereomer: ^{1}H NMR (400 MHz) δ 7.48 (d, *J* = 2.5 Hz, 1 H, C15-H), 7.33 (d, *J* = 8.9 Hz, 2 H, C18+C22-H), 7.21 (d, *J* = 2.9 Hz, 1 H, C13-H), 6.91 (d, *J* = 8.9 Hz, 2 H, C19+C21-H), 6.88 (m, 1 H, C12-H), 5.68 (d, *J* = 6.5 Hz, 1 H, C9-H), 5.03 (s, 2 H, C16-H), 4.13 (s, 3 H, C6-H), 3.94 (s, 3 H, C5-H), 3.86 (s, 1 H, C4-OH), 3.81 (s, 3 H, C23-H), 3.45 (d, *J* = 6.5 Hz, 1 H, C9-OH); Minor diastereomer: ^{1}H NMR (400 MHz) δ 7.46 (d, *J* = 2.4 Hz, 1 H, C15-H), 7.34 (d *J* = 8.9 Hz, 2 H, C18+C22-H), 7.23 (d, *J* = 2.4 Hz, 1 H, C13-H), 6.91 (d, *J* = 8.9 Hz, 2 H, C19+C21-H), 6.86 (m, 1 H, C12-H), 5.68 (d, *J* = 6.5 Hz, 1 H, C9-H), 5.03 (s, 2 H, C16-H), 4.13 (s, 3 H, C6-H), 3.94 (s, 3 H, C5-H), 3.81 (s, 3 H, C23-H), 3.73 (s, 1 H, C4-OH), 3.41 (d, *J* = 6.2 Hz, 1 H, C9-OH); ^{13}C NMR (150 MHz) δ 180.5 (C1), 180.4 (C1), 164.5 (C3), 164.4 (C3), 159.6 x 2 (C2), 154.3 x 2 (C11), 135.6 x 2 (C2), 130.1 x 2 (C14), 129.2 x 2 (C13), 129.1 (C18+C22), 129.0 (C18+C22), 128.1 (C17), 127.8 x 2 (C15), 126.0 x 2 (C10), 114.1 (C19+C21), 113.6 x 2 (C12), 88.5 x 2 (C8), 80.0, x 2 (C7), 78.4 x 2 (C16), 70.6 (C16), 70.5 (C16), 60.4 (C9), 60.3 (C6), 60.1 (C6), 58.6 (C5), 55.3 x 2 (C23).



5-((5-Chloro-2-(4-methoxybenzyloxy)phenyl)(hydroxy)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75d). ALN-4-151. Thermolysis of **2.74d** required 1.5 h. Flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford **2.75d** (78%) as a red oil; ^{1}H NMR (600 MHz, CD_3OD) δ 7.39 (d, *J* = 2.0 Hz, 1 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 9.0 Hz, 1 H), 7.04 (d, *J* = 8.7 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.25 (d, *J* = 1.3 Hz, 1 H), 5.98 (s, 1 H), 4.98, 4.96 (ABq, *J* = 11.2 Hz, 2 H), 3.95 (s, 3 H), 3.87 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.7, 184.3, 161.1, 155.5, 149.5, 146.3, 146.1, 133.3, 130.9, 130.5, 129.9, 129.8, 128.6, 126.8, 115.0, 114.9, 71.6, 64.7, 61.7, 61.6, 55.7; IR (CH_2Cl_2) 3486, 2950, 1656, 1603, 1246 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{46}H_{42}O_{14}NaCl_2]^+$ (2M+Na), 911.1844; found, 911.1842.

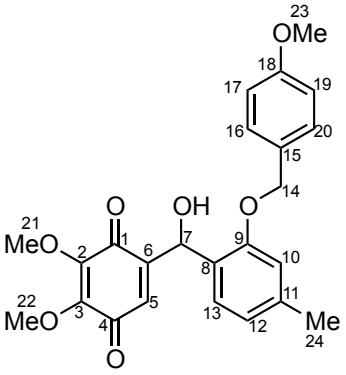
NMR Assignments. ^{1}H NMR (600 MHz, CD_3OD) δ 7.39 (d, *J* = 2.0 Hz, 1 H, C13-H), 7.26 (d, *J* = 8.7 Hz, 2 H, C16+C20-H), 7.25 (d, *J* = 9.0 Hz, 1 H, C11-H), 7.04 (d, *J* = 8.7 Hz, 1 H, C10-H), 6.86 (d, *J* = 8.8 Hz, 2 H, C17+C19-H), 6.25 (d, *J* = 1.3 Hz, 1 H, C5-H), 5.98 (s, 1 H, C7-H), 4.98, 4.96 (ABq, *J* = 11.2 Hz, 2 H, C14-H), 3.95 (s, 3 H, C22-H), 3.87 (s, 3 H, C21-H), 3.79 (s, 3 H, C23-H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.7 (C4), 184.3 (C1), 161.1 (C18), 155.5 (C9), 149.5 (C6), 146.3 (C2), 146.1 (C3), 133.3 (C8), 130.9 (C5), 130.5 (C16+C20), 129.9 (C15), 129.8 (C1), 128.6 (C13), 126.8 (C12), 115.0 (C10), 114.9 (C17+C19), 71.6 (C14), 64.7 (C7), 61.7 (C21), 61.6 (C22), 55.7 (C23).



5-(Hydroxy(4-methoxy-2-(4-methoxybenzyloxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75e). ALN-4-102. Yield of **2.74e**: 52%. Thermolysis required 1 h. Flash column chromatography eluting with Hexanes:EtOAc (3:1 to 1:1) to afford **2.75e** (63%) as a red oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (d, *J* = 8.8 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.39 (d, *J* = 1.5 Hz, 1 H), 6.00 (d, *J* = 1.3 Hz, 1 H), 4.97 (s, 2 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.76 (s, 3 H); ^{13}C NMR (125 Hz, CD_3OD) δ 185.9, 184.7, 162.2, 160.9, 158.1, 150.4, 146.3, 146.1, 130.5, 130.4, 130.3, 129.6, 123.2, 114.9, 106.0. 101.1, 71.2, 65.0, 61.7, 55.8, 55.7; IR (CH_2Cl_2) 3493, 2949, 1656, 1605, 1515, 1251, 828 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{24}H_{25}O_8]^+$ (M+H), 441.1549; found, 441.1541.

NMR Assignments. ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (d, *J* = 8.8 Hz, 2 H, C16+C20-H), 7.22 (d, *J* = 8.8 Hz, 1 H, C13-H), 6.86 (d, *J* = 8.8 Hz, 2 H, C17+C19-H), 6.60 (d, *J* = 2.4 Hz, 1 H, C10-H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1 H, C12-H), 6.39 (d, *J* = 1.5 Hz, 1 H, C5-H), 6.00 (d, *J* = 1.3 Hz, 1 H, C7-H), 4.97 (s, 2 H, C14-H), 3.94 (s, 3 H, C21-H), 3.85 (s, 3 H, C22-H), 3.78 (s, 3 H, C23-H), 3.76 (s, 3 H, C24-H); ^{13}C NMR (125 Hz, CD_3OD) δ 185.9 (C4), 184.7 (C1), 162.2 (C11), 160.9 (C18), 158.1 (C9), 150.4 (C6), 146.3 (C2), 146.1 (C3), 130.5 (C15), 130.4 (C16+C20), 130.3 (C5), 129.6 (C13), 123.2

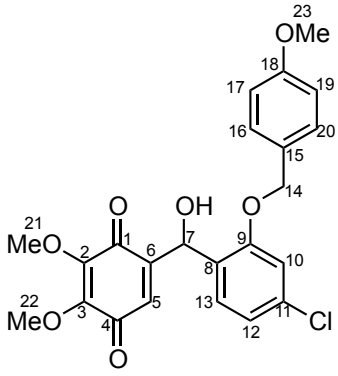
(C8), 114.9 (C17+C19), 106.0 (C12), 101.1 (C10), 71.2 (C14), 65.0 (C7), 61.7 (C22), 61.6 (C21), 55.8 (C24), 55.7 (C23).



5-(Hydroxy(2-(4-methoxybenzyloxy)-4-methylphenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75f). ALN-4-27. Yield of **2.74f**: 62%. Thermolysis required 1.5 h. Flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford **2.75f** (73%) as a red oil; ^{1}H NMR (600 MHz, CD_3OD) δ 7.29 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 7.7 Hz, 1 H), 6.89 (s, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 7.7 Hz, 1 H), 6.33 (s, 1 H), 6.02 (s, 1 H), 4.99, 4.97 (ABq, *J* = 11.2 Hz, 2 H), 3.94 (s, 3 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.9, 184.6, 160.9, 157.0, 150.4, 146.4, 146.1, 140.5, 130.6, 130.5, 130.4, 128.6, 127.9, 122.4, 114.9, 114.4, 71.2, 65.0, 61.6, 61.57, 55.7, 21.5; IR (CH_2Cl_2) 3487, 2919, 1656, 1605, 1515, 1249, 1030 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{24}H_{24}O_7]^{+\bullet}$ ($M^{+\bullet}$), 424.1522; found, 424.1517.

NMR Assignments. ^{1}H NMR (600 MHz, CD_3OD) δ 7.29 (d, *J* = 8.7 Hz, 2 H, C16+C20-H), 7.23 (d, *J* = 7.7 Hz, 1 H, C13-H), 6.89 (s, 1 H, C10-H), 6.87 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.79 (d, *J* = 7.7 Hz, 1 H, C12-H), 6.33 (s, 1 H, C5-H), 6.02 (s, 1 H,C7-H), 4.99, 4.97 (ABq, *J* = 11.2 Hz, 2 H, C14-H), 3.94 (s, 3 H, C22-H), 3.86 (s, 3 H, C21-H), 3.79 (s, 3 H, C23-H), 2.33 (s, 3 H, C24-H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.9

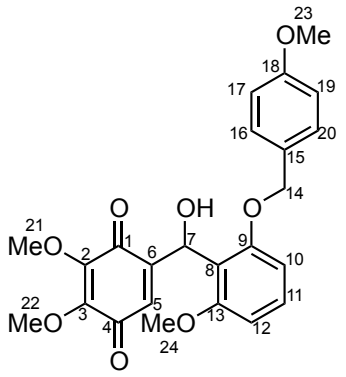
(C4), 184.6 (C1), 160.9 (C18), 157.0 (C9), 150.4 (C6), 146.4 (C2), 146.1 (C3), 140.5 (C11), 130.6 (C15), 130.5 (C5), 130.4 (C16+C20), 128.6 (C13), 127.9 (C8), 122.4 (C12), 114.9 (C17+C19), 114.4 (C10), 71.2 (C14), 65.0 (C7), 61.6 (C21), 61.57 (C22), 55.7 (C23), 21.5 (C24).



5-((4-Chloro-2-(4-methoxybenzyloxy)phenyl)(hydroxy)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75g). ALN-4-278. Yield of **2.74g**: 53%. Thermolysis required 2.5 h. Flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford **2.75g** (60%) as a red oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.35 (d, *J* = 8.2 Hz, 1 H), 7.29 (d *J* = 8.7 Hz, 2 H), 7.08 (d, *J* = 2.0 Hz, 1 H), 6.97 (dd, *J* = 8.1, 2.0 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.33 (s, 1 H), 5.99 (s, 1 H), 5.01, 4.97 (ABq, *J* = 11.1 Hz, 2 H), 3.95 (s, 3 H), 3.86 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.8, 184.5, 161.1, 157.6, 149.7, 146.3, 146.1, 135.5, 130.8, 130.5, 130.0, 129.9, 129.7, 121.7, 115.0, 114.1, 71.6, 64.7, 61.7, 61.6, 55.7; IR (CH_2Cl_2) 3480, 2949, 1656, 1602, 1515, 1246 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{23}H_{22}O_7Cl]^+$ (M+H), 445.1049; found, 445.1040.

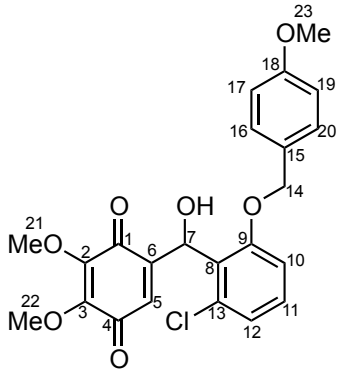
NMR Assignments. ^{1}H NMR (500 MHz, CD_3OD) δ 7.35 (d, *J* = 8.2 Hz, 1 H, C10-H), 7.29 (d *J* = 8.7 Hz, 2 H, C16+C20-H), 7.08 (d, *J* = 2.0 Hz, 1 H, C13-H), 6.97 (dd, *J* = 8.1, 2.0 Hz, 1 H, C12-H), 6.87 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.33 (s, 1 H,

C5-H), 5.99 (s, 1 H, C7-H), 5.01, 4.97 (ABq, J = 11.1 Hz, 2 H, C14-H), 3.95 (s, 3 H, C22-H), 3.86 (s, 3 H, C21-H), 3.79 (s, 3 H, C23-H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.8 (C4), 184.5 (C1), 161.1 (C18), 157.6 (C9), 149.7 (C6), 146.3 (C2), 146.1 (C3), 135.5 (C11), 130.8 (C5), 130.5 (C16+C20), 130.0 (C8), 129.9 (C10), 129.7 (C15), 121.7 (C12), 115.0 (C17+C19), 114.1 (C13), 71.6 (C14), 64.7 (C7), 61.7 (C21), 61.6 (C22), 55.7 (C23).



5-(Hydroxy(2-methoxy-6-(4-methoxybenzyloxy)phenyl)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75h). ALN-4-295. Yield of **2.74h**: 65%. Thermolysis required 2.5 h. Flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford **2.75h** (83%) as a red oil; ^{1}H NMR (600 MHz, CD_3OD) δ 7.27 (d, J = 8.7 Hz, 2 H), 7.24 (t, J = 8.4 Hz, 1 H), 6.84 (d, J = 8.7 Hz, 2 H), 6.69 (d, J = 8.4 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 1 H), 6.55 (d, J = 2.3 Hz, 1 H), 6.08 (d, J = 2.4 Hz, 1 H), 4.94, 4.88 (ABq, J = 10.7 Hz, 2 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.8, 184.9, 161.0, 159.8, 158.4, 151.8, 146.0, 145.9, 130.8, 130.7, 129.9, 129.1, 119.1, 115.1, 106.9, 105.7, 71.8, 63.3, 61.6, 61.4, 56.5, 55.7; IR (CH_2Cl_2) 3512, 2943, 1656, 1602, 1249, 1098 cm^{-1}; HRMS (CI) m/z calculated for $[C_{24}H_{25}O_8]^+$ (M+H), 441.1549; found, 441.1547.

NMR Assignments. ^{1}H NMR (600 MHz, CD_3OD) δ 7.27 (d, *J* = 8.7 Hz, 2 H, C16+C20-H), 7.24 (t, *J* = 8.4 Hz, 1 H, C11-H), 6.84 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.69 (d, *J* = 8.4 Hz, 1 H, C10-H), 6.67 (d, *J* = 8.4 Hz, 1 H, C12-H), 6.55 (d, *J* = 2.3 Hz, 1 H, C5-H), 6.08 (d, *J* = 2.4 Hz, 1 H, C7-H), 4.94, 4.88 (ABq, *J* = 10.7 Hz, 2 H, C14-H), 3.87 (s, 3 H, C22-H), 3.84 (s, 3 H, C24-H), 3.80 (s, 3 H, C23-H), 3.78 (s, 3 H, C21-H); ^{13}C NMR (150 MHz, CD_3OD) δ 185.8 (C4), 184.9 (C1), 161.0 (C18), 159.8 (C13), 158.4 (C9), 151.8 (C6), 146.0 (C2), 145.9 (C3), 130.8 (C11), 130.7 (C16+C20), 129.9 (C16), 129.1 (C5), 119.1 (C8), 115.1 (C17+C19), 106.9 (C10), 105.7 (C12), 71.8 (C14), 63.3 (C7), 61.6 (C21), 61.4 (C22), 56.5 (C24), 55.7 (C23).



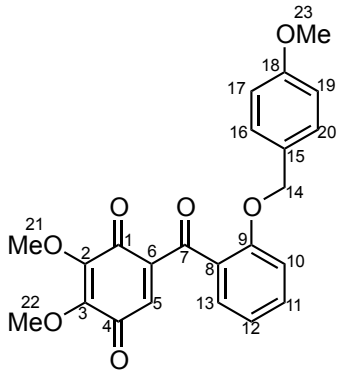
5-((6-Chloro-2-(4-methoxybenzyloxy)phenyl)(hydroxy)methyl)-2,3-dimethoxycyclohexa-2,5-diene-1,4-dione (2.75i). ALN-4-289. Yield of **2.74i**: 65%. Thermolysis required 2.5 h. Flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford **2.75i** (62%) as a red oil; ^{1}H NMR (500 MHz, CD_3OD) δ 7.24-7.22 (comp, 3 H), 7.07 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.54 (d, *J* = 2.4 Hz, 1 H), 6.05 (d, *J* = 2.4 Hz, 1 H), 4.92, 4.84 (ABq, *J* = 10.4 Hz, 2 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.76 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.5, 184.8, 161.2, 158.8, 151.0, 146.0, 145.7, 136.5, 130.9, 130.7, 129.3, 129.1, 128.9, 123.4, 115.2, 112.5, 72.1, 66.6, 61.6, 61.3, 55.7; IR (CH_2Cl_2) 3476, 2950, 2839, 1655, 1604, 1251,

1028 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{23}H_{22}O_7Cl]^{+\bullet}$ ($M^{+\bullet}$), 444.0976; found, 444.0974.

NMR Assignments. ^1H NMR (500 MHz, CD_3OD) δ 7.24-7.22 (comp, 3 H, C16+C20/C11-H), 7.07 (dd, *J* = 8.1, 1.0 Hz, 1 H, C12-H), 7.00 (d, *J* = 8.1 Hz, 1 H, C10-H), 6.84 (d, *J* = 8.7 Hz, 2 H, C17+C19-H), 6.54 (d, *J* = 2.4 Hz, 1 H, C5-H), 6.05 (d, *J* = 2.4 Hz, 1 H, C7-H), 4.92, 4.84 (ABq, *J* = 10.4 Hz, 2 H, C14-H), 3.86 (s, 3 H, C22-H), 3.82 (s, 3 H, C23-H), 3.76 (s, 3 H, C21-H); ^{13}C NMR (125 MHz, CD_3OD) δ 185.5 (C1), 184.8 (C2), 161.2 (C18), 158.8 (C9), 151.0 (C6), 146.0 (C3), 145.7 (C2), 136.5 (C13), 130.9 (C16+C20), 130.7 (C11), 129.3 (C5), 129.1 (C15), 128.9 (C8), 123.4 (C12), 115.2 (C17+C19), 112.5 (C10), 72.1 (C14), 66.6 (C7), 61.6 (C21), 61.3 (C22), 55.7 (C23).

Representative Procedure for Preparation of Ketones 2.76a–i.

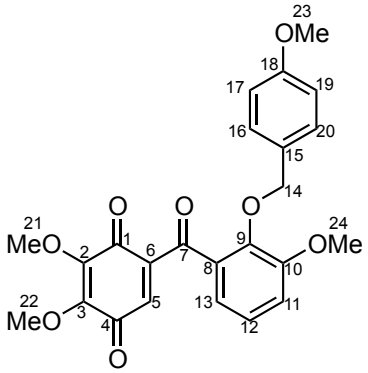
Note: Keto-quinones **2.75a-i** were subjected to the deprotection/cyclization without purification.



2,3-Dimethoxy-5-[2-(4-methoxybenzyloxy)benzoyl]-[1,4]benzoquinone (2.76a). ALN-4-257. A solution of Jones' reagent (0.061 mL, 0.16 mmol) was added to a stirred solution of **2.75a** (0.056 g, 0.14 mmol) in acetone (4 mL) at 0 °C. The solution was stirred for 1 h, at which time 2-propanol (~1 mL) was added, and the reaction was

warmed to room temperature. The reaction was diluted with H_2O (5 mL) and brine (10 mL). The aqueous layer was washed with Et_2O (2 x 20 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 0.053 g (96%) of **2.76a** as a red solid (Hexanes/EtOAc): mp 114-115 °C; ^{1}H NMR (400 MHz) δ 7.95 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.03 (d, *J* = 8.2 Hz, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 6.46 (s, 1 H), 4.89 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (75 MHz) δ 189.7, 183.7, 181.7, 159.7, 158.5, 146.4, 144.8, 143.2, 135.7, 130.5, 129.8, 128.6, 126.7, 125.9, 121.2, 114.1, 112.5, 70.8, 61.0, 60.5, 55.1; IR (CH_2Cl_2) 2951, 1653, 1596, 1517, 1454, 1246 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{23}H_{20}NaO_7]^+$ (M+Na), 431.1107; found, 431.1102.

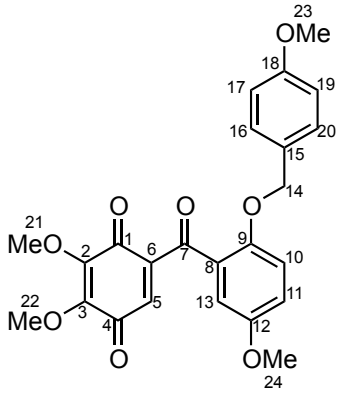
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.95 (dd, *J* = 7.7, 1.4 Hz, 1 H, C13-H), 7.58 (t, *J* = 7.6 Hz, 1 H, C11-H), 7.17 (d, *J* = 8.6 Hz, 2 H, C16+C20-H), 7.12 (t, *J* = 7.5 Hz, 1 H, C12-H), 7.03 (d, *J* = 8.2 Hz, 1 H, C10-H), 6.83 (d, *J* = 8.6 Hz, 2 H, C17+C19-H), 6.46 (s, 1 H, C5-H), 4.29 (s, 2 H, C14-H), 3.85 (s, 3 H, C21/C22), 3.83 (s, 3 H, C21/C22), 3.77 (s, 3 H, C23-H).



2,3-Dimethoxy-5-[3-methoxy-2-(4-methoxybenzyloxy)benzoyl]-[1,4]benzoquinone (2.76b). ALN-3-294. Isolated in 93% as a red oil; ^{1}H NMR (400

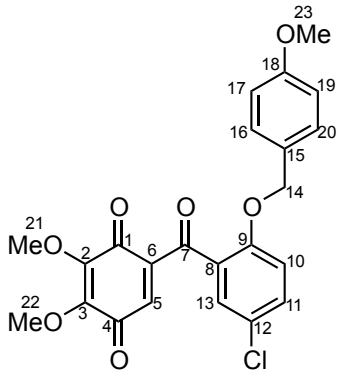
MHz) δ 7.48 (dd, *J* = 7.2, 2.4 Hz, 1 H), 7.21-7.16 (comp, 4 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.51 (s, 1 H), 4.83 (s, 2 H), 3.92 (s, 3 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.70 (s, 3 H); IR (CH_2Cl_2) 2950, 1658, 1597, 1515, 1268 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{24}H_{23}O_8]^+$ (M+H), 439.1387; found, 439.1387.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.48 (dd, *J* = 7.2, 2.4 Hz, 1 H, C13-H), 7.21-7.16 (comp, 4 H), 6.82 (d, *J* = 8.5 Hz, 2 H, C17+C19-H), 6.51 (s, 1 H, C5-H), 4.83 (s, 2 H, C14-H), 3.92 (s, 3 H, C24), 3.84 (s, 3 H, C21/C22), 3.82 (s, 3 H, C21/C22), 3.70 (s, 3 H, C23-H).



2,3-Dimethoxy-5-[5-methoxy-2-(4-methoxybenzyloxy)benzoyl]-[1,4]benzoquinone (2.76c). ALN-4-263. Isolated in 92% as a red solid; ^{1}H NMR (400 MHz) δ 7.46 (d, *J* = 3.4 Hz, 1 H), 7.16 (d, *J* = 8.9 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 6.98 (d, *J* = 8.9 Hz, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 6.46 (s, 1 H), 4.84 (s, 2 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.76 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.3, 183.6, 181.7, 159.6, 153.8, 153.1, 146.4, 144.8, 143.2, 129.7, 128.6, 126.9, 126.0, 123.0, 114.3, 114.0, 112.8, 71.4, 61.0, 60.5, 55.6, 55.1; IR (CH_2Cl_2) 2949, 2839, 1652, 1598, 1219, 1036 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{24}H_{23}O_8]^+$ (M+H), 439.13929; found, 439.13874.

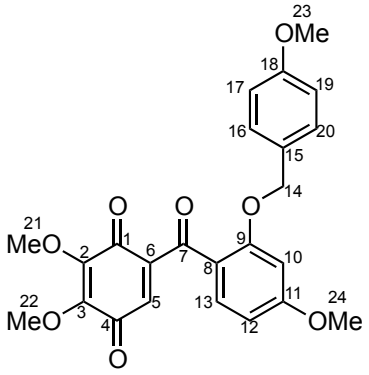
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.46 (d, *J* = 3.4 Hz, 1 H, C13-H), 7.16 (d, *J* = 8.9 Hz, 1 H, C11-H), 7.15 (d, *J* = 8.6 Hz, 2 H, C16+C20-H), 6.98 (d, *J* = 8.9 Hz, 1 H, C10-H), 6.86 (d, *J* = 8.6 Hz, 2 H, C17+C19-H), 6.46 (s, 1 H, C5-H), 4.84 (s, 2 H, C14-H), 3.85 (s, 3 H, C21/C22/C23-H), 3.84 (s, 3 H, C21/C22/C23-H), 3.83 (s, 3 H, C21/C22/C23-H), 3.76 (s, 3 H, C23-H).



5-[5-Chloro-2-(4-methoxybenzyloxy)benzoyl]-2,3-dimethoxy-[1,4]benzoquinone (2.76d). ALN-3-299. Isolated in 93% as an orange solid: mp 125-126 °C; ^{1}H NMR (400 MHz) δ 7.89 (d, *J* = 2.7 Hz, 1 H), 7.52 (dd, *J* = 8.7, 2.7 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 6.97 (d, *J* = 8.7 Hz, 1 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.48 (s, 1 H), 4.87 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.78 (s, 3 H); ^{13}C NMR (100 MHz) δ 188.7, 183.5, 181.7, 159.9, 156.9, 145.7, 145.0, 143.2, 135.1, 130.1, 129.8, 129.3, 127.1, 126.8, 126.3, 114.2, 114.1, 71.3, 61.1, 60.7, 55.2; IR (CH_2Cl_2) 2927, 1651, 1613, 1594, 1271, 1250 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{23}H_{19}O_7NaCl]^+$ (M+Na), 465.07115; found, 465.07099.

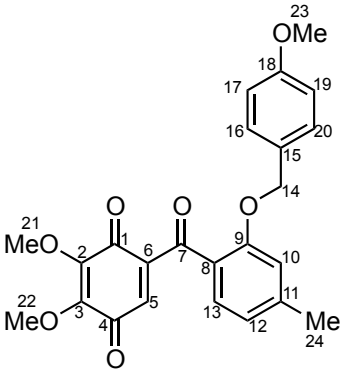
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.89 (d, *J* = 2.7 Hz, 1 H, C13-H), 7.52 (dd, *J* = 8.7, 2.7 Hz, 1 H, C11-H), 7.15 (d, *J* = 8.6 Hz, 2 H, C16+C20-H), 6.97 (d, *J* = 8.7 Hz, 1 H, C10-H), 6.82 (d, *J* = 8.6 Hz, 2 H, C17+C19-H), 6.48 (s, 1 H, C5-H), 4.87

(s, 2 H, C14-H), 3.85 (s, 3 H, C21/C22-H), 3.83 (s, 3 H, C21/C22-H), 3.78 (s, 3 H, C23-H).



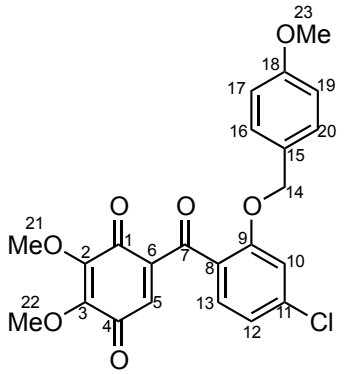
2,3-Dimethoxy-5-[4-methoxy-2-(4-methoxybenzyloxy)benzoyl]-[1,4]benzoquinone (2.76e). ALN-3-271. Isolated in 99% as a red-orange solid: mp 129-130 °C; ^{1}H NMR (400 MHz) δ 7.98 (d, *J* = 8.9 Hz, 1 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.64 (dd, *J* = 8.9, 2.1 Hz, 1 H), 6.49 (d, *J* = 2.1 Hz, 1 H), 6.40 (s, 1 H), 4.85 (s, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (100 MHz) δ 188.0, 183.9, 182.0, 166.2, 160.5, 159.8, 147.2, 144.8, 143.1, 132.6, 130.0, 128.0, 126.5, 119.2, 114.1, 106.4, 98.8, 70.9, 61.1, 60.5, 55.7, 55.1; IR (CH_2Cl_2) 2949, 2841, 1655, 1596, 1517, 1261 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{24}H_{23}O_8]^+$ (M+H), 439.13874; found, 439.13885.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.98 (d, *J* = 8.9 Hz, 1 H, C13-H), 7.16 (d, *J* = 8.6 Hz, 2 H, C16+C20-H), 6.82 (d, *J* = 8.6 Hz, 2 H, C17+C19-H), 6.64 (dd, *J* = 8.9, 2.1 Hz, 1 H, C12-H), 6.49 (d, *J* = 2.1 Hz, 1 H, C10-H), 6.40 (s, 1 H, C5-H), 4.85 (s, 2 H, C14-H), 3.89 (s, 3 H, C24-H), 3.84 (s, 3 H, C21/C22-H), 3.83 (s, 3 H, C21/C22-H), 3.75 (s, 3 H, C23-H).



2,3-Dimethoxy-5-[2-(4-methoxybenzyloxy)4-methylbenzoyl]-[1,4]benzoquinone (2.76f). ALN-4-33. Isolated in 98% as a yellow oil; ^{1}H NMR (400 MHz) δ 7.86 (d, *J* = 7.9 Hz, 1 H), 7.16 (d, *J* = 8.9 Hz, 2 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 6.84-6.81 (comp, 3 H), 6.43 (s, 1 H), 4.87 (s, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 2.42 (s, 3 H); IR (CH_2Cl_2) 2951, 1654, 1601, 1516, 1252, 1171 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{24}H_{23}O_7]^+$ (M+H), 423.1438; found, 423.1439.

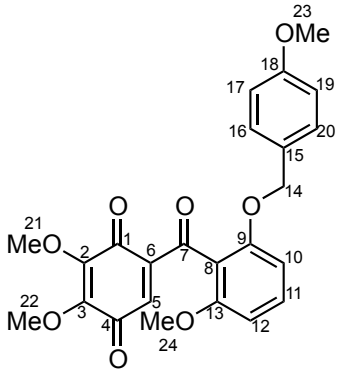
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.86 (d, *J* = 7.9 Hz, 1 H, C13-H), 7.16 (d, *J* = 8.9 Hz, 2 H, C16+C20-H), 6.93 (d, *J* = 8.2 Hz, 1 H, C12-H), 6.84-6.81 (comp, 3 H, C17+C19+C10-H), 6.43 (s, 1 H, C5-H), 4.87 (s, 2 H, C14-H), 3.84 (s, 3 H, C21/C22-H), 3.83 (s, 3 H, C21/C22-H), 3.75 (s, 3 H, C23-H), 2.42 (s, 3 H, C24-H).



5-[4-Chloro-2-(4-methoxybenzyloxy)benzoyl]-2,3-dimethoxy-[1,4]benzoquinone (2.76g). ALN-5-280. Isolated in 89% as an orange solid

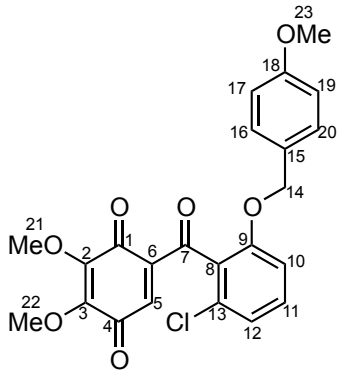
(Hexanes/EtOAc): 135-136 °C; ^{1}H NMR (400 MHz) δ 7.88 (d, *J* = 8.6 Hz, 1 H), 7.16 (d, *J* = 8.9 Hz, 2 H), 7.17 (dd, *J* = 8.4, 1.7 Hz, 1 H), 7.04 (d, *J* = 1.7 Hz, 1 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 6.46 (s, 1 H), 4.88 (s, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (400 MHz) δ 188.8, 183.6, 181.8, 160.0, 158.8, 146.0, 144.9, 143.1, 141.7, 131.6, 129.9, 129.1, 126.0, 124.6, 121.7, 114.2, 113.2, 71.3, 61.1, 60.6, 55.2; IR (CH_2Cl_2) 2951, 1654, 1591, 1516, 1244, 1136 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{23}H_{19}O_7NaCl]^+$ (M+Na), 465.0717; found, 465.0710.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.88 (d, *J* = 8.6 Hz, 1 H, C13-H), 7.16 (d, *J* = 8.9 Hz, 2 H, C16+C20-H), 7.17 (dd, *J* = 8.4, 1.7 Hz, 1 H, C12-H), 7.04 (d, *J* = 1.7 Hz, 1 H, C10-H), 6.83 (d, *J* = 8.9 Hz, 2 H, C17+C19-H), 6.46 (s, 1 H, C5-H), 4.88 (s, 2 H, C14-H), 3.85 (s, 3 H, C21/C22-H), 3.83 (s, 3 H, C21/C22-H), 3.77 (s, 3 H, C23-H).



2,3-Dimethoxy-5-[2-methoxy-6-(4-methoxybenzyloxy)benzoyl]-[1,4]benzoquinone (2.76h). ALN-5-31. Isolated in 96%; ^{1}H NMR (400 MHz) δ 7.37 (t, *J* = 8.4 Hz, 1 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.65 (s, 1 H), 6.62 (d, *J* = 8.4 Hz, 2 H), 4.92 (s, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.80 (s, 3 H); IR (CH_2Cl_2) 2950, 2841, 1660, 1631, 1595, 1472, 1252, 1103 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{24}H_{23}O_8]^+$ (M+H), 439.1387; found, 439.1390.

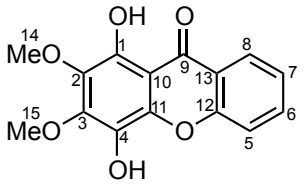
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.37 (t, *J* = 8.4 Hz, 1 H, C11-H), 7.18 (d, *J* = 8.8 Hz, 2 H, C16+C20-H), 6.82 (d, *J* = 8.8 Hz, 2 H, C17+C19-H), 6.65 (s, 1 H, C5-H), 6.62 (d, *J* = 8.4 Hz, 2 H, C10+C12-H), 4.92 (s, 2 H, C14-H), 3.93 (s, 3 H, C24-H), 3.87 (s, 3 H, C21/C22-H), 3.82 (s, 3 H, C21/C22-H), 3.80 (s, 3 H, C23-H).



5-[2-Chloro-6-(4-methoxy-benzyloxy)benzoyl]-2,3-dimethoxy-[1,4]benzoquinone (2.76i). ALN-5-83. Isolated in 99%; ^{1}H NMR (400 MHz) δ 7.34 (t, *J* = 8.2 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 7.08 (d, *J* = 7.5 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 6.75 (s, 1 H), 4.91 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 3.80 (s, 3 H); IR (CH_2Cl_2) 3418, 2925, 1680, 1611, 1590, 1448, 1250 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{23}H_{19}O_7NaCl]^+$ (M+Na), 465.0717; found, 465.0711.

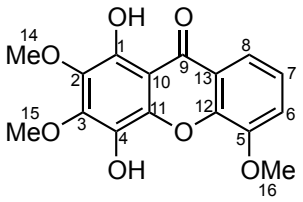
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.34 (t, *J* = 8.2 Hz, 1 H, C11-H), 7.15 (d, *J* = 8.6 Hz, 2 H, C16+C20-H), 7.08 (d, *J* = 7.5 Hz, 1 H, C12-H), 6.90 (d, *J* = 8.2 Hz, 1 H, C10-H), 6.82 (d, *J* = 8.0 Hz, 2 H, C17+C19-H), 6.75 (s, 1 H, C5-H), 4.91 (s, 2 H, C14-H), 3.95 (s, 3 H, C21/C22-H), 3.90 (s, 3 H, C21/C22-H), 3.80 (s, 3 H, C23-H).

Representative Procedure for Preparation of Xanthones 2.27a–d,g.



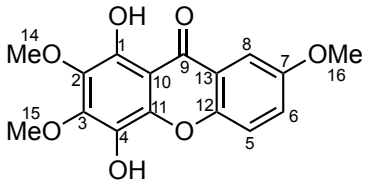
1,4-Dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (2.27a). ALN-3-248. The unpurified keto-quinone **2.76a** (0.053 g, 0.13 mmol) was dissolved in CH_2Cl_2 (5 mL) and sparged with Ar for 3 min whereupon TFA (0.099 mL, 0.15 g, 1.3 mmol) was added. Sparging was continued for 1 min at which time the reaction was stirred at room temperature under Ar for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford 0.037 g (99%) of **2.27a** as a yellow solid (Et_2O/Hexanes): mp 180-181 °C; ^{1}H NMR (400 MHz) δ 12.39 (s, 1 H), 8.27 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.75 (td, *J* = 8.0, 2.0 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H), 5.43 (s, 1 H), 4.19 (s, 3 H), 3.98 (s, 3 H); ^{13}C NMR (100 MHz) δ 181.7, 156.0, 148.0, 147.1, 139.4, 135.4, 134.8, 128.7, 126.0, 124.1, 120.1, 117.9, 105.2, 61.7, 61.1; IR (CH_2Cl_2) 3385, 2922, 2851, 1651, 1464 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{13}O_6]^+$ (M+H), 289.0712; found, 289.0713.

NMR Assignments. ^{1}H NMR (400 MHz) δ 12.39 (s, 1 H, C1-OH), 8.27 (dd, *J* = 7.8, 1.2 Hz, 1 H, C8-H), 7.75 (td, *J* = 8.0, 2.0 Hz, 1 H, C6-H), 7.56 (d, *J* = 7.6 Hz, 1 H, C5-H), 7.40 (t, *J* = 8.0 Hz, 1 H, C7-H), 5.43 (s, 1 H, C4-OH), 4.19 (s, 3 H, C15), 3.98 (s, 3 H, C14); ^{13}C NMR (100 MHz) δ 181.7 (C9), 156.0 (C12), 148.0 (C11), 147.1 (C3), 139.4 (C1), 135.4 (C6), 134.8 (C2), 128.7 (C4), 126.0 (C8), 124.1 (C7), 120.1 (C13), 117.9 (C5), 105.2 (C10), 61.7 (C15), 61.1 (C14).



1,4-Dihydroxy-2,3,5-trimethoxy-9*H*-xanthen-9-one (2.27b). ALN-4-228. Flash column chromatography eluting with Hexanes:EtOAc (3:1 to 2:1) to afford **2.27b** (83%) as a yellow solid (Hexanes/EtOAc): mp 184-185 °C; ^{1}H NMR (400 MHz) δ 12.29 (s, 1 H), 7.82 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 7.24 (dd, *J* = 7.9, 1.7 Hz, 1 H), 5.55 (s, 1 H), 4.16 (s, 3 H), 4.02 (s, 3 H), 3.97 (s, 3 H); ^{13}C NMR (100 MHz) δ 181.7, 148.6, 147.6, 147.3, 146.3, 139.4, 135.0, 129.1, 123.6, 120.9, 116.6, 115.7, 105.0, 61.7, 61.1, 56.4; IR (CH_2Cl_2) 3498, 2941, 1590, 1497, 1377, 1029, 748 cm^{-1}; HRMS (CI) calculated for $[C_{16}H_{15}O_7]^+$ (M+H), 319.0818; found, 319.0812.

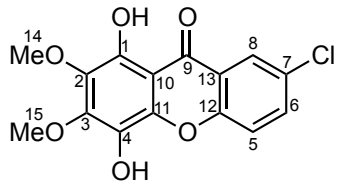
NMR Assignments. ^{1}H NMR (400 MHz) δ 12.29 (s, 1 H, C1-OH), 7.82 (dd, *J* = 7.9, 1.7 Hz, 1 H, C8-H), 7.30 (t, *J* = 7.9 Hz, 1 H, C7-H), 7.24 (dd, *J* = 7.9, 1.7 Hz, 1 H, C6-H), 5.55 (s, 1 H, C4-OH), 4.16 (s, 3 H, C15-H), 4.02 (s, 3 H, C14-H), 3.97 (s, 3 H, C16-H); ^{13}C NMR (100 MHz) δ 181.7 (C9), 148.6 (C5), 147.6 (C12), 147.3 (C3), 146.3 (C1), 139.4 (C11), 135.0 (C2), 129.1 (C4), 123.6 (C7), 120.9 (C13), 116.6 (C8), 115.7 (C6), 105.0 (C10), 61.7 (C15), 61.1 (C14), 56.4 (C16).



1,4-Dihydroxy-2,3,7-trimethoxy-9*H*-xanthen-9-one (2.27c). ALN-4-270. Flash column chromatography eluting with Hexanes:EtOAc (5:1) to afford **2.27c** (88%) as a yellow solid (Hexanes/EtOAc): mp 156-157 °C; ^{1}H NMR (500 MHz) δ 12.44 (s, 1

H), 7.62 (d, *J* = 3.2 Hz, 1 H), 7.49 (d, *J* = 9.2 Hz, 1 H), 7.35 (dd, *J* = 9.2, 3.1 Hz, 1 H), 5.40 (s, 1 H), 4.18 (s, 3 H), 3.98 (s, 3 H), 3.92 (s, 3 H); ^{13}C NMR (125 MHz) δ 181.4, 156.1, 151.1, 147.9, 143.2 x 2, 132.4, 132.0, 125.4, 120.3, 119.4, 104.9, 104.6, 62.1, 61.5, 56.0; IR (CH_2Cl_2) 3347, 2951, 1580, 1487, 745 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{15}O_7]^+$ (M+H), 319.0818; found, 319.0814.

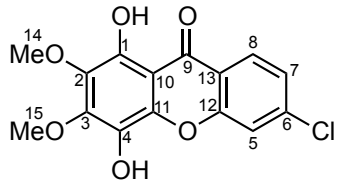
NMR Assignments. ^{1}H NMR (500 MHz) δ 12.44 (s, 1 H, C1-OH), 7.62 (d, *J* = 3.2 Hz, 1 H, C8-H), 7.49 (d, *J* = 9.2 Hz, 1 H, C5-H), 7.35 (dd, *J* = 9.2, 3.1 Hz, 1 H, C6-H), 5.40 (s, 1 H, C4-OH), 4.18 (s, 3 H, C15-H), 3.98 (s, 3 H, C14-H), 3.92 (s, 3 H, C16-H); ^{13}C NMR (125 MHz) δ 181.4 (C9), 156.1 (C7), 151.1 (C12), 147.9 (C3), 143.2 x 2 (C1+C11), 132.4 (C4), 132.0 (C2), 125.4 (C6), 120.3 (C13), 119.4 (C5), 104.9 (C8), 104.6 (C10), 62.1 (C14), 61.5 (C15), 56.0 (C16).



7-Chloro-1,4-dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (2.27d). ALN-3-301. Flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford **2.27d** (99%) as a red solid (Et_2O/Hexanes): mp 215-216 °C; ^{1}H NMR (600 MHz) δ 12.16 (br s, 1 H), 8.20 (d, *J* = 2.4 Hz, 1 H), 7.65 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.49 (d, *J* = 9.0 Hz, 1 H), 4.17 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (100 MHz) δ 180.6, 154.4, 148.0, 147.4, 139.1, 135.5, 135.0, 129.9, 128.7, 125.3, 121.0, 119.6, 104.9, 61.8, 61.1; IR (CH_2Cl_2) 3352, 2949, 1655, 1606, 1212, 1032 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{12}O_6Cl]$ (M+H), 323.0322; found, 323.0325.

NMR Assignments. ^{1}H NMR (600 MHz) δ 12.16 (br s, 1 H, C1-OH), 8.20 (d, *J* = 2.4 Hz, 1 H, C8-H), 7.65 (dd, *J* = 9.0, 2.4 Hz, 1 H, C6-H), 7.49 (d, *J* = 9.0 Hz, 1 H, C5-

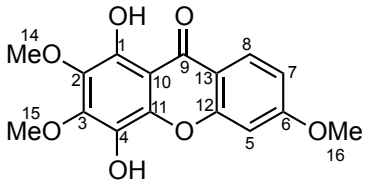
H), 4.17 (s, 3 H), C15-H, 3.95 (s, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 180.6 (C9), 154.4 (C12), 148.0 (C1), 147.4 (C3), 139.1 (C11), 135.5 (C6), 135.0 (C2), 129.9 (C7), 128.7 (C4), 125.3 (C8), 121.0 (C13), 119.6 (C5), 104.9 (C10), 61.8 (C15), 61.1 (C14).



6-Chloro-1,4-dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (2.27g). ALN-4-281. Flash column chromatography eluting with Hexanes:EtOAc (5:1 to 3:1) to afford **2.27g** (71%) as yellow plates (Hexanes/Et_2O): mp 212-213 °C; ^{1}H NMR (500 MHz) δ 12.23 (s, 1 H), 8.17 (d, *J* = 9.0 Hz, 1 H), 7.56 (d, *J* = 1.9 Hz, 1 H), 7.33 (dd, *J* = 9.0, 1.9 Hz, 1 H), 5.40 (s, 1 H), 4.17 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (125 MHz) δ 181.0, 156.2, 148.1, 147.4, 141.5, 139.1, 135.1, 128.8, 127.3, 125.0, 118.7, 118.0, 105.0, 61.8, 61.1; IR (CH_2Cl_2) 3345, 2933, 1578, 1254, 1031 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{15}H_{12}O_6Cl]^+$ (M+H), 323.03169; found, 323.0318.

NMR Assignments. ^{1}H NMR (500 MHz) δ 12.23 (s, 1 H, C1-OH), 8.17 (d, *J* = 9.0 Hz, 1 H, C8-H), 7.56 (d, *J* = 1.9 Hz, 1 H, C5-H), 7.33 (dd, *J* = 9.0, 1.9 Hz, 1 H, C7-H), 5.40 (s, 1 H, C4-OH), 4.17 (s, 3 H, C15-H), 3.95 (s, 3 H, C15-H); ^{13}C NMR (125 MHz) δ 181.0 (C9), 156.2 (C12), 148.1 (C11), 147.4 (C3), 141.5 (C6), 139.1 (C1), 135.1 (C2), 128.8 (C4), 127.3 (C8), 125.0 (C5), 118.7 (C13), 118.0 (C7), 105.0 (C10), 61.8 (C15), 61.1 (C14).

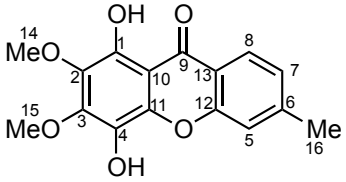
Representative Procedure for Preparation of Xanthones 2.27e,f,h,i.



1,4-Dihydroxy-2,3,6-trimethoxy-9*H*-xanthen-9-one (2.27e). ALN-3-271. TFA (0.12 mL, 0.17 g, 1.5 mmol) was added to a stirred solution of unpurified **2.76e** (0.066 g, 0.15 mmol) in CH_2Cl_2 (3 mL) at room temperature. The solution was previously sparged with Ar for 3 min prior to the addition of TFA, and 1 min after TFA was added. The solution was then stirred under Ar for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 mL). The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The mixture (1:2) of **2.80e:2.27e** was dissolved in acetone (6 mL) and stirred in the presence of K_2CO_3 (0.10 g, 0.75 mmol) for 1.5 h. The mixture was filtered through a celite plug eluting with acetone, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with Hexanes:EtOAc (5:1 to 3:1) to afford 0.041 g (84%) of **2.27e** as yellow cubes (Hexanes/Et_2O): mp 194-195 °C; ^{1}H NMR (500 MHz) δ 12.52 (s, 1 H), 8.16 (d, J = 8.8 Hz, 1 H), 6.97-6.93 (comp, 2 H), 5.43 (s, 1 H), 4.17 (s, 3 H), 3.97 (s, 3 H), 3.92, (s, 3 H); ^{13}C NMR (125 MHz) δ 180.9, 165.6, 158.1, 148.0, 146.6, 139.4, 134.9, 128.5, 127.4, 113.9, 113.8, 105.0, 100.1, 61.7, 61.1, 56.0; IR (CH_2Cl_2) 2924, 1607, 1573, 956 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{13}O_7]^-$ (M-1), 317.1025; found, 317.1023.

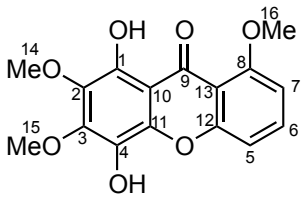
NMR Assignments. ^{1}H NMR (500 MHz) δ 12.52 (s, 1 H, C1-OH), 8.16 (d, J = 8.8 Hz, 1 H, C8-H), 6.97-6.93 (comp, 2 H, C5/7-H), 5.43 (s, 1 H, C4-OH), 4.17 (s, 3 H, C15-H), 3.97 (s, 3 H, C14-H), 3.92, (s, 3 H, C16-H); ^{13}C NMR (125 MHz) δ 180.9 (C9), 165.6 (C6), 158.1 (C12), 148.0 (C1), 146.6 (C3), 139.4 (C11), 134.9 (C2), 128.5 (C4),

127.4 (C8), 113.9 (C13), 113.8 (C7), 105.0 (C10), 100.1 (C5), 61.7 (C15), 61.1 (C14), 56.0 (C16).



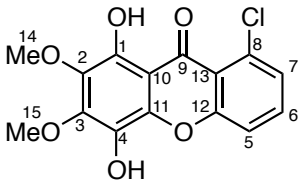
1,4-Dihydroxy-2,3-dimethoxy-6-methyl-9*H*-xanthen-9-one (2.27f). ALN-4-38. Flash column chromatography eluting with Hexanes:EtOAc (5:1) to afford **2.27f** (78%) as a yellow powder (Hexanes/Et_2O): mp 197-198 °C; ^{1}H NMR (400 MHz) δ 12.45 (s, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 7.36 (s, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 5.42 (s, 1 H), 4.17 (s, 3 H), 3.97 (s, 3 H), 2.51 (s, 3 H); ^{13}C NMR (100 MHz) δ 181.6, 156.1, 147.9, 147.1, 147.0, 139.4, 134.7, 128.7, 125.7 x 2, 117.8, 117.7, 105.1, 61.7, 61.1, 22.1; IR (CH_2Cl_2) 3398, 2921, 1612, 1235, 1029 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{15}O_6]^+$ (M+H), 303.0869; found, 303.0867.

NMR Assignments. ^{1}H NMR (400 MHz) δ 12.45 (s, 1 H, C1-H), 8.13 (d, *J* = 8.0 Hz, 1 H, C8-H), 7.36 (s, 1 H, C5-H), 7.20 (d, *J* = 8.0 Hz, 1 H, C7-H), 5.42 (s, 1 H, C4-H), 4.17 (s, 3 H, C15-H), 3.97 (s, 3 H, C14-H), 2.51 (s, 3 H, C16-H); ^{13}C NMR (100 MHz) δ 181.6 (C9), 156.1 (C12), 147.9 (C1), 147.1 (C6), 147.0 (C3), 139.4 (C11), 134.7 (C2), 128.7 (C4), 125.7 x 2 (C8+C5), 117.8 (C13), 117.7 (C7), 105.1 (C10), 61.7 (C15), 61.1 (C14), 22.1 (C16).



1,4-Dihydroxy-2,3,8-trimethoxy-9*H*-xanthen-9-one (2.27h). ALN-4-255. Flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford **2.27h** (64%) as a yellow solid (Hexanes/*tert*-butylmethyl ether): mp 174-175 °C (dec.); ^{1}H NMR (600 MHz) δ 12.70 (s, 1 H), 7.60 (t, *J* = 8.4 Hz, 1 H), 7.10 (dd, *J* = 8.4, 1.0 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 5.33 (s, 1 H), 4.14 (s, 3 H), 4.02 (s, 3 H), 3.93 (s, 3 H); ^{13}C NMR (150 MHz) δ 182.1, 160.8, 158.0, 148.3, 146.7, 138.6, 135.6, 134.9, 128.0, 110.7, 110.0, 105.7 x 2, 61.6, 61.1, 56.5; IR (CH_2Cl_2) 3384, 2930, 1607, 1482, 1100 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{15}O_7]^+$ (M+H), 319.0818; found, 319.0816.

NMR Assignments. ^{1}H NMR (600 MHz) δ 12.70 (s, 1 H, C1-OH), 7.60 (t, *J* = 8.4 Hz, 1 H, C6-H), 7.10 (dd, *J* = 8.4, 1.0 Hz, 1 H, C5-H), 6.78 (d, *J* = 8.4 Hz, 1 H, C7-H), 5.33 (s, 1 H, C4-OH), 4.14 (s, 3 H, C15-H), 4.02 (s, 3 H, C16-H), 3.93 (s, 3 H, C14-H); ^{13}C NMR (150 MHz) δ 182.1 (C9), 160.8 (C8), 158.0 (C12), 148.3 (C11), 146.7 (C3), 138.6 (C1), 135.6 (C6), 134.9 (C2), 128.0 (C4), 110.7 (C13), 110.0 (C5), 105.7 x 2 (C10+C7), 61.6 (C15), 61.1 (C14), 56.5 (C16).

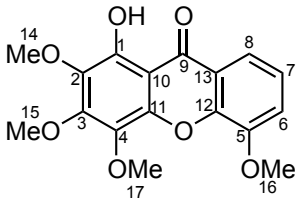


8-Chloro-1,4-dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (2.27i). ALN-5-159. Flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford **2.27i** (61%) as orange cubes (Hexanes/EtOAc): mp 207-208 °C; ^{1}H NMR (500 MHz) δ 12.39 (br s, 1 H), 7.58 (t, *J* = 8.5 Hz, 1 H), 7.48 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.34 (dd, *J* = 8.5, 1.2 Hz, 1 H), 5.38 (br s, 1 H), 4.18 (s, 3 H), 3.96 (s, 3 H); ^{13}C NMR (150 MHz) δ 181.1, 157.7, 148.3, 147.2, 138.3, 135.0, 134.3, 134.2, 128.1, 127.4, 117.2 x 2, 105.4, 61.7, 61.1; IR

(CH_2Cl_2) 3402, 2926, 1592, 1456, 1026 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{15}H_{11}O_6Cl]^{+\bullet}$ ($M^{+\bullet}$), 322.0244; found, 322.0244.

NMR Assignments. ^1H NMR (500 MHz) δ 12.39 (br s, 1 H, C1-OH), 7.58 (t, *J* = 8.5 Hz, 1 H, C6-H), 7.48 (dd, *J* = 8.5, 1.2 Hz, 1 H, C5-H), 7.34 (dd, *J* = 8.5, 1.2 Hz, 1 H, C7-H), 5.38 (br s, 1 H, C4-OH), 4.18 (s, 3 H, C15-H), 3.96 (s, 3 H, C14-H); ^{13}C NMR (150 MHz) δ 181.1 (C9), 157.7 (C12), 148.3 (C1), 147.2 (C3), 138.3 (C11), 135.0 (C2), 134.3 (C6), 134.2 (C8), 128.1 (C4), 127.4 (C7), 117.2 x 2 (C13/C5), 105.4 (C10), 61.7 (C15), 61.1 (C14).

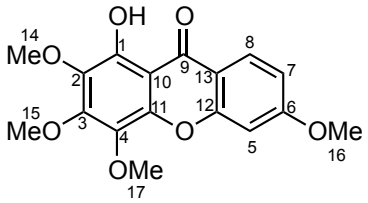
Representative procedure for phenol methylation.



1-Hydroxy-2,3,4,5-tetramethoxy-9*H*-xanthen-9-one (2.87). ALN-4-250. K_2CO_3 (0.063 g, 0.45 mmol) was added to a stirred solution of **2.27b** (0.016 g, 0.050 mmol) and Me_2SO_4 (0.038 mL, 0.051 g, 0.40 mmol) in acetone (5.0 mL) at room temperature. The heterogeneous mixture was stirred at room temperature for 5.5 h at which time the reaction was quenched with H_2O (10 mL), brine (10 mL), and 1 M HCl (1 mL). The aqueous layer was washed with Et_2O (2 x 20 mL), and the combined organic layers were washed with brine (1 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (5:1) to afford 0.014 g (84%) of **2.87** as a yellow powder (aqueous EtOH): mp 149-150 °C; lit. 155-156 °C;[16] ^1H NMR (600 MHz)

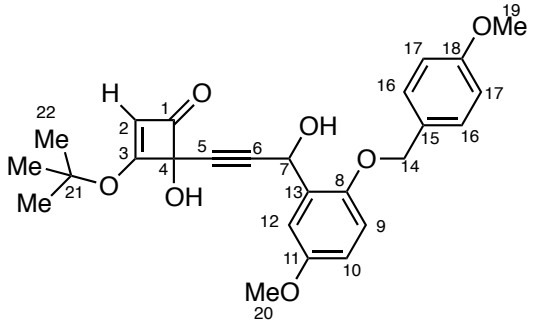
δ 12.57 (s, 1 H), 7.81 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 1 H), 7.25 (dd, *J* = 8.0, 1.5 Hz, 1 H), 4.15 (s, 3 H), 4.03 (s, 3 H), 4.02 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (150 MHz) δ 181.7, 154.2, 150.6, 148.8, 146.4, 145.7, 135.5, 132.8, 123.7, 120.9, 116.6, 116.0, 105.1, 61.9, 61.7, 61.2, 56.5; IR (CH_2Cl_2) 2939, 1587, 1365, 1268, 1051 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{17}O_7]^+$ (M+H), 333.0974; found, 333.0978.

NMR Assignments. ^{1}H NMR (600 MHz) δ 12.57 (s, 1 H, C1-OH), 7.81 (dd, *J* = 8.0, 1.5 Hz, 1 H, C8-H), 7.31 (t, *J* = 8.0 Hz, 1 H, C7-H), 7.25 (dd, *J* = 8.0, 1.5 Hz, 1 H, C6-H), 4.15 (s, 3 H, C15-H), 4.03 (s, 3 H, C16-H), 4.02 (s, 3 H, C17-H), 3.95 (s, 3 H, C14-H); ^{13}C NMR (150 MHz) δ 181.7 (C9), 154.2 (C3), 150.6 (C11), 148.8 (C5), 146.4 (C12), 145.7 (C1), 135.5 (C2), 132.8 (C4), 123.7 (C7), 120.9 (C13), 116.6 (C8), 116.0 (C6), 105.1 (C10), 61.9 (C17), 61.7 (C15), 61.2 (C14), 56.5 (C16).



1-Hydroxy-2,3,4,6-tetramethoxy-9*H*-xanthen-9-one (2.88). ALN-3-273. Flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford **2.88** (99%) as a yellow powder (aqueous EtOH): mp 102-103 °C; ^{1}H NMR (500 MHz) δ 12.77 (s, 1 H), 8.16-8.14 (m, 1 H), 6.96 (d, *J* = 2.3 Hz, 1 H), 6.94 (d, *J* = 2.3 Hz, 1 H), 4.14 (s, 3 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR (125 MHz) δ 180.8, 165.6, 158.8, 153.8, 151.0, 145.8, 135.6, 132.4, 127.4, 113.9, 113.8, 104.9, 100.2, 62.1, 61.7, 61.2, 56.0; IR (CH_2Cl_2) 2938, 1623, 1459, 1052 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{17}O_7]^+$ (M+H), 333.0974; found, 333.0973.

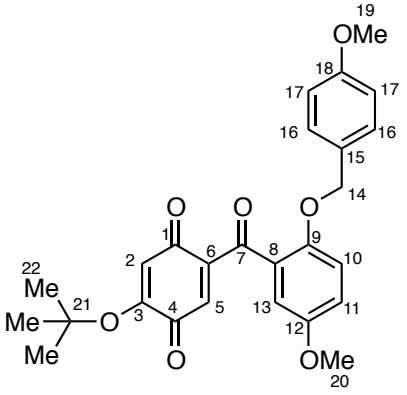
NMR Assignments. ^{1}H NMR (500 MHz) δ 12.77 (s, 1 H, C1-OH), 8.16-8.14 (m, 1 H, C11-H), 6.96 (d, *J* = 2.3 Hz, 1 H, C10-H), 6.94 (d, *J* = 2.3 Hz, 1 H, C8-H), 4.14 (s, 3 H, C15-H), 3.96 (s, 3 H, C16-H), 3.95 (s, 3 H, C14-H), 3.94 (s, 3 H, C17-H); ^{13}C NMR (125 MHz) δ 180.8 (C13), 165.6 (C9), 158.8 (C7), 153.8 (C3), 151.0 (C5), 145.8 (C1), 135.6 (C2), 132.4 (C4), 127.4 (C11), 113.9 (C12), 113.8 (C10), 104.9 (C6), 100.2 (C8), 62.1 (C14), 61.7 (C15), 61.2 (C16), 56.0 (C17).



3-(*tert*-Butoxy)-4-hydroxy-4-(3-hydroxy-3-(5-methoxy-2-((4-methoxybenzyl) oxy)phenyl)prop-1-yn-1-yl)cyclobut-2-enone (2.93). ALN-4-32. A solution of *n*-BuLi (0.93 mL, 1.7 mmol, 1.81 M in Hexanes) was added dropwise over 2 min to a solution of **2.73c** (0.24 g, 0.080 mmol) in DME at -50 ˚C. The reaction was stirred for 30 min whereupon a solution of **2.94** (0.14 g, 0.088 mmol) was added *via* syringe pump over 30 min. The reaction was stirred for 30 min, and then a solution of AcOH in THF (3 mL, 1 M) was added, and the reaction was warmed to ambient temperature. The reaction was concentrated under reduced pressure; the resulting oil was dissolved in Et_2O (15 mL), stirred for 20 min, and then vacuum filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1 to 2:1) to afford 0.093 g (26%) of **2.93** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.35 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 3.2 Hz, 1 H), 6.91-6.86 (comp, 3 H),

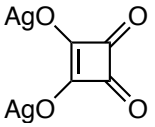
6.79-6.76 (m, 1 H), 5.71 (s, 1 H), 5.23 (s, 1 H), 5.03-4.95 (comp, 2 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 1.49 (s, 9 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.35 (d, *J* = 8.8 Hz, 2 H, C16-H), 7.11 (d, *J* = 3.2 Hz, 1 H, C12-H), 6.91-6.86 (comp, 3 H, C17+C9-H), 6.79-6.76 (m, 1 H, C10-H), 5.71 (s, 1 H, C2-H), 5.23 (s, 1 H, C7-H), 5.03-4.95 (comp, 2 H, C14-H), 3.79 (s, 3 H, C19/C20-H), 3.75 (s, 3 H, C19/C20-H), 1.49 (s, 9 H, C22-H).

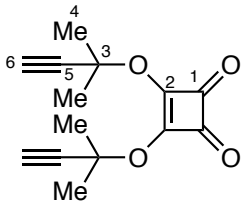


2-(*tert*-Butoxy)-5-(5-methoxy-2-((4-methoxybenzyl)oxy)benzoyl)cyclohexa-2,5-diene-1,4-dione (2.95). ALN-4-37. A solution of Jones reagent (0.009 mL, 0.024 mmol) was added to a solution of **2.92** (0.009 g, 0.019 mmol) in acetone at 0 ˚C. The reaction was stirred for 1 h at which time 2-propanol (~0.5 mL) and brine (1 mL) were added. The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 0.009 g (99%) of **2.95** as a red oil; ^{1}H NMR (400 MHz) δ 7.40 (d, *J* = 3.2 Hz, 1 H), 7.08-7.07 (comp, 3 H), 6.91 (d, *J* = 9.2 Hz, 1 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 6.47 (s, 1 H), 5.67 (s, 1 H), 4.81 (s, 2 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 1.36 (s, 9 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.40 (d, *J* = 3.2 Hz, 1 H, C13-H), 7.08-7.07 (comp, 3 H, C16+C11-H), 6.91 (d, *J* = 9.2 Hz, 1 H, C10-H), 6.72 (d, *J* = 8.8 Hz, 2 H, C17-H), 6.47 (s, 1 H, C5-H), 5.67 (s, 1 H, C2-H), 4.81 (s, 2 H, C14-H), 3.79 (s, 3 H, C19/C20-H), 3.77 (s, 3 H, C19/C20-H), 1.36 (s, 9 H, C22-H).

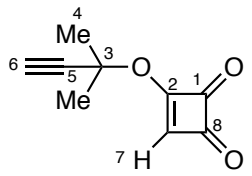


Squaric acid disilver salt (2.97). ALN-4-63. Prepared according to literature procedure.[143]



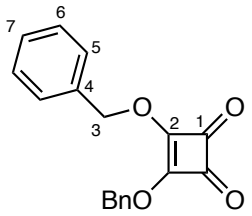
3,4-Bis((2-methylbut-3-yn-2-yl)oxy)cyclobut-3-ene-1,2-dione (2.104). ALN-4-202. A solution of **2.103** (2.3 g, 2.6 mL, 23 mmol) in Et_2O (10 mL) was added to a mixture of **2.97** (1.5 g, 4.6 mmol) in Et_2O (20 mL) at room temperature. The mixture was heated under reflux for 2 h and then stirred at ambient temperature for 12 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (1:1) to afford 0.62 g (56%) of **2.104** as a colorless solid (EtOAc/Hexanes): mp 82-83 °C; ^{1}H NMR (400 MHz) δ 2.69 (s, 2 H), 1.88 (s, 12 H); ^{13}C NMR (100 MHz) δ 187.9, 184.7, 82.9, 79.2, 75.6, 29.4; IR (CH_2Cl_2) 2994, 2123, 1809, 1743, 1584, 1369, 1119 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{14}H_{15}O_5]^+$ (M+H), 247.0970; found, 247.0970.

NMR Assignments. ^{1}H NMR (400 MHz) δ 2.69 (s, 2 H, C6-H), 1.88 (s, 12 H, C4-H); ^{13}C NMR (100 MHz) δ 187.9 (C1), 184.7 (C2), 82.9 (C5), 79.2 (C6), 75.6 (C3), 29.4 (C4).

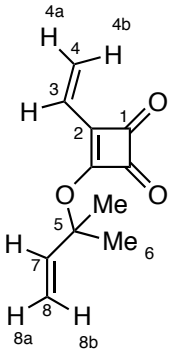


3-((2-Methylbut-3-yn-2-yl)oxy)cyclobut-3-ene-1,2-dione (2.101). ALN-4-205. $LiAl(O\textit{t}Bu)_3H$ (0.44 mL, 0.49 mmol, 1.1 M in THF) was added to a solution of **2.104** (0.10 g, 0.41 mmol) in THF (12 mL) at 0 ˚C. The solution was stirred for 40 min whereupon the reaction was warmed to ambient temperature over 30 min. Trifluoroacetic anhydride (0.12 g, 0.085 mL, 0.61 mmol) was added, and the reaction was stirred an additional 25 min whereupon saturated aqueous NH_4Cl (10 mL) and saturated aqueous Rochelle's salt (5 mL) were added. The aqueous layer was washed with Et_2O (2 x 20 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (4:1 to 2:1) to afford 0.035 g (52%) of **2.101** as a yellow oil; ^{1}H NMR (400 MHz) δ 8.73 (s, 1 H), 2.80 (s, 1 H), 1.81 (s, 6 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 8.73 (s, 1 H, C7-H), 2.80 (s, 1 H, C6-H), 1.81 (s, 6 H, C4-H).

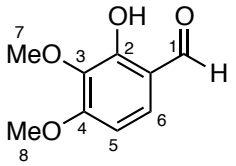


3,4-Bis(benzyloxy)cyclobut-3-ene-1,2-dione (2.98). ALN-4-64. Prepared according to literature procedure.[145]

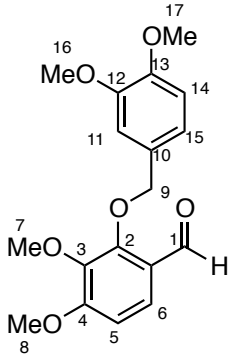


3-(2-Methylbut-3-en-2-yloxy)-4-vinylcyclobut-3-ene-1,2-dione (2.101). ALN-2-156. Vinyl squarate **2.108** (0.050 g, 0.36 mmol) in THF (3.6 mL) was transferred *via* cannula to a solution of *n*-BuLi (0.34 mL, 0.72 mmol, 2.12 M in Hexanes) and 2-methylbut-3-en-2-ol (**2.109**) (0.62 g, 0.76 mL, 7.2 mmol) at 0° C. After 3 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the aqueous mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (8 g SiO_2) eluting with Hexanes:EtOAc (6:1) to afford 0.019 g (27%) of **2.101** as a yellow oil; ^{1}H NMR (400 MHz) δ 6.65 (dd, *J* = 17.6, 14.2 Hz, 1 H), 6.50 (dd, *J* = 17.2, 1.8 Hz, 1 H), 6.17 (dd, *J* = 17.2, 10.6 Hz, 1 H), 5.85 (dd, *J* = 12.8, 2.0 Hz, 1 H), 5.38 (d, *J* = 17.2 Hz, 1 H), 5.26 (d, *J* = 11.2 Hz, 1 H), 1.72 (s, 6 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 6.65 (dd, *J* = 17.6, 14.2 Hz, 1 H, C3-H), 6.50 (dd, *J* = 17.2, 1.8 Hz, 1 H, C4-H4b), 6.17 (dd, *J* = 17.2, 10.6 Hz, 1 H, C7-H), 5.85 (dd, *J* = 12.8, 2.0 Hz, 1 H, C4-H4a), 5.38 (d, *J* = 17.2 Hz, 1 H, C8-H8b), 5.26 (d, *J* = 11.2 Hz, 1 H, C8-H8a), 1.72 (s, 6 H, C6-H).



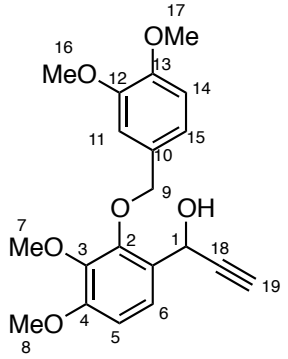
2-Hydroxy-3,4-dimethoxybenzaldehyde (2.117). ALN-4-204. Prepared according to literature procedures.[275]



2-((3,4-Dimethoxybenzyl)oxy)-3,4-dimethoxybenzaldehyde (2.118). ALN-4-208. K_2CO_3 (2.2 g, 16 mmol) was added to a solution of **2.117** (0.98 g, 5.4 mmol) and DMB-Cl (1.2 g, 6.4 mmol) in DMF (15 mL) at room temperature. The mixture was stirred 2 h and then placed in a preheated oil bath (90 ˚C) and stirred for 20 h. The reaction was cooled to ambient temperature, and diluted with H_2O (15 mL). The aqueous layer was washed with $PhCH_3$ (3 x 20 mL), and the combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The solid thus obtained was recrystallized from Hexanes/EtOAc to afford 1.5 g

(85%) of **2.118** as a cream-colored powder; ^{1}H NMR (400 MHz) δ 10.11 (s, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 6.95-6.93 (comp, 2 H), 6.83 (d, *J* = 8.8 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 5.16 (s, 2 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H).

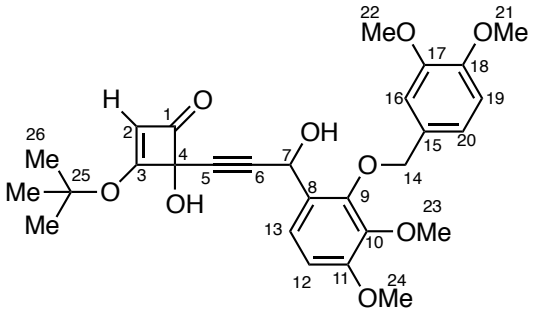
NMR Assignments. ^{1}H NMR (400 MHz) δ 10.11 (s, 1 H, C1-H), 7.58 (d, *J* = 8.0 Hz, 1 H, C6-H), 6.95-6.93 (comp, 2 H, C11+C15-H), 6.83 (d, *J* = 8.8 Hz, 1 H, C14-H), 6.77 (d, *J* = 8.0 Hz, 1 H, C5-H), 5.16 (s, 2 H, C9-H), 3.96 (s, 3 H, C8/C7/C16/C17-H), 3.93 (s, 3 H, C8/C7/C16/C17-H), 3.88 (s, 3 H, C8/C7/C16/C17-H), 3.87 (s, 3 H, C8/C7/C16/C17-H).



1-(2-((3,4-Dimethoxybenzyl)oxy)-3,4-dimethoxyphenyl)prop-2-yn-1-ol (2.114). ALN-4-211. Ethynyl magnesium bromide (11 mL, 5.4 mmol, 0.5 M in THF) was added to a solution of **2.118** (1.5 g, 4.5 mmol) in THF (9 mL) at 0 ˚C. The reaction was stirred for 2.5 h whereupon saturated aqueous NH_4Cl (10 mL) and H_2O (5 mL) were added. The layers were separated, and the aqueous layer was washed with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by filtering through a plug of silica gel eluting with Hexanes:EtOAc (1:1) to afford 1.6 g (99%) of **2.114** as a colorless oil; ^{1}H NMR (400 MHz) δ 7.24 (d, *J* = 8.0 Hz, 1 H), 7.05-7.03 (comp, 2 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 5.51 (br s, 1 H),

5.15 (s, 2 H), 3.91-3.89 (comp, 12 H), 2.72 (br s, 1 H), 2.60 (s, 1 H); ^{13}C NMR (100 MHz) δ 153.9, 149.8, 148.9, 148.7, 141.9, 129.5, 126.8, 122.1, 121.1, 111.8, 110.8, 107.1, 83.8, 75.4, 73.8, 60.6, 60.0, 55.8, 55.7 55.6; IR (CH_2Cl_2) 3478, 3282, 2938, 2359, 1597, 1517, 1265, 1094 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{20}H_{22}O_6]^{+\bullet}$ ($M^{+\bullet}$), 358.1416; found, 358.1417.

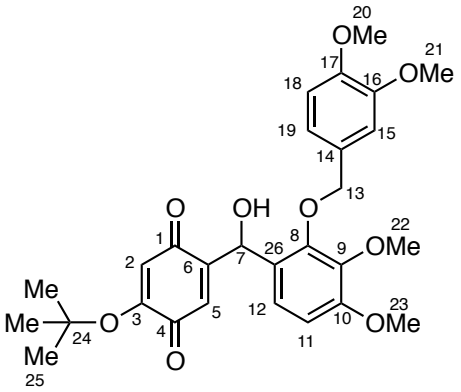
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.24 (d, *J* = 8.0 Hz, 1 H, C6-H), 7.05-7.03 (comp, 2 H, C15+C11-H), 6.87 (d, *J* = 8.8 Hz, 1 H, C14-H), 6.70 (d, *J* = 8.0 Hz, 1 H, C5-H), 5.51 (br s, 1 H, C1-H), 5.15 (s, 2 H, C9-H), 3.91-3.89 (comp, 12 H, C7+C8+C16+C17-H), 2.72 (br s, 1 H, C1-OH), 2.60 (s, 1 H, C19-H).



3-(*tert*-Butoxy)-4-(3-(2-((3,4-dimethoxybenzyl)oxy)-3,4-dimethoxyphenyl)-3-hydroxyprop-1-yn-1-yl)-4-hydroxycyclobut-2-enone (2.119). ALN-4-216. *n*-BuLi (0.60 mL, 1.4 mmol, 2.37 M in Hexanes) was added to a solution of **2.114** (0.23 g, 0.65 mmol) in THF (5 mL) at 0 ˚C. The solution was cooled to -78 ˚C and stirred for 10 min whereupon a solution of **2.94** (0.13 g, 0.84 mmol) in THF (2 mL) was transferred *via* cannula to the anion solution. The reaction was stirred at -78 ˚C for 30 min, warmed to -40 ˚C, and stirred for 1.5 h. The reaction was removed from the cooling bath, warmed to ambient temperature, and then quenched with saturated aqueous NH_4Cl (15 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 15 mL), and the combined organic layers

were washed with brine (1 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (4:1 to 1:1) to afford 0.11 g (32%) of **2.119** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.21-7.18 (m, 1 H), 7.05-7.01 (comp, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 5.57 (m, 1 H), 5.23 (s, 1 H), 5.08 (s, 2 H), 3.87-3.84 (comp, 12 H), 1.45 (s, 9 H).

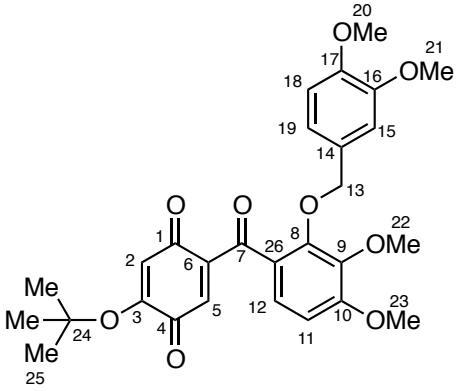
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.21-7.18 (m, 1 H, C13-H), 7.05-7.01 (comp, 2 H, C16+C20-H), 6.84 (d, *J* = 8.0 Hz, 1 H, C19-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C12-H), 5.57 (m, 1 H, C2-H), 5.23 (s, 1 H, C7-H), 5.08 (s, 2 H, C14-H), 3.87-3.84 (comp, 12 H, C21+C22+C23+C24-H), 1.45 (s, 9 H, C26-H).



2-(*tert*-Butoxy)-5-((2-((3,4-dimethoxybenzyl)oxy)-3,4-dimethoxyphenyl) (hydroxy)methyl)cyclohexa-2,5-diene-1,4-dione (2.120). ALN-4-220. A solution of **2.119** (0.32 g, 0.62 mmol) in MeCN (6 mL) was degassed with Ar for 4 min. The reaction was then heated under reflux for 20 min, cooled to room temperature by removing from the heating bath, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford 0.008 g (25%) of **2.120** as a red oil; ^{1}H NMR (400 MHz) δ 6.99-6.95 (comp, 2

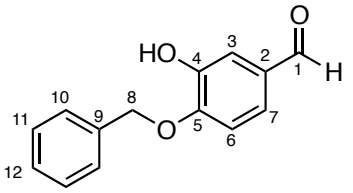
H), 6.86 (d, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.31 (s, 1 H), 5.98 (s, 2 H), 5.11 (s, 2 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 1.52 (s, 9 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 6.99-6.95 (comp, 2 H, Ar-H), 6.86 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.77 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.70 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.31 (s, 1 H, C2-H), 5.98 (s, 2 H, C7+C5-H), 5.11 (s, 2 H, C13-H), 3.91 (s, 3 H, C20/C21/C22/C23-H), 3.88 (s, 3 H, C20/C21/C22/C23-H), 3.87 (s, 3 H, C20/C21/C22/C23-H), 3.85 (s, 3 H, C20/C21/C22/C23-H), 1.52 (s, 9 H, C25-H).

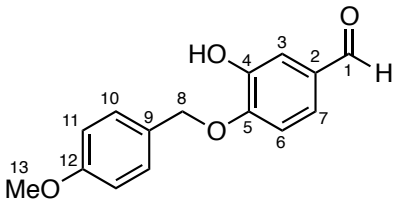


2-(*tert*-Butoxy)-5-(2-((3,4-dimethoxybenzyl)oxy)-3,4-dimethoxybenzoyl) cyclohexa-2,5-diene-1,4-dione (2.121). ALN-4-222. A solution of Jones reagent (0.007 mL, 0.019 mmol, 2.67 M) was added to a solution of **2.120** (0.008 g, 0.016 mmol) in acetone (2 mL) at 0 ˚C. The solution was stirred for 30 min, and then quenched with 2-propanol (~0.5 mL). The aqueous layer was washed with Et_2O (2 x 15 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. No purification was performed; ^{1}H NMR (400 MHz) δ 7.72 (d, *J* = 8.8 Hz, 1 H), 6.83 (d, *J* = 8.8 Hz, 1 H), 6.75-6.74 (comp, 3 H), 6.50 (s, 1 H), 5.78 (s, 1 H), 4.88 (s, 2 H), 3.96-3.84 (comp, 12 H), 1.40 (s, 9 H).

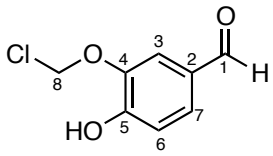
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.72 (d, *J* = 8.8 Hz, 1 H, C12-H), 6.83 (d, *J* = 8.8 Hz, 1 H, C11-H), 6.75-6.74 (comp, 3 H, C18+C19+C15-H), 6.50 (s, 1 H, C2-H), 5.78 (s, 1 H, C5-H), 4.88 (s, 2 H, C13-H), 3.96-3.84 (comp, 12 H, C20+C21+C22+C23-H), 1.40 (s, 9 H, C25-H).



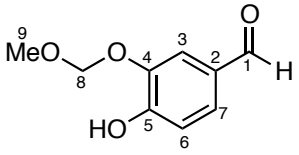
4-(Benzyloxy)-3-hydroxybenzaldehyde (2.135). Prepared according to literature procedures.[276]



3-Hydroxy-4-((4-methoxybenzyl)oxy)benzaldehyde (2.138). Prepared according to literature procedures.[276]

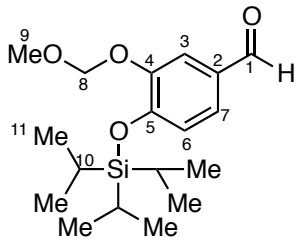


3-(Chloromethoxy)-4-hydroxybenzaldehyde (2.141). ALN-7-24. Prepared according to literature procedures.[153]

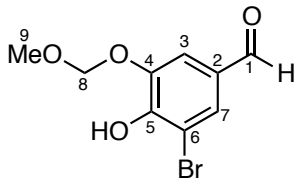


4-Hydroxy-3-(methoxymethoxy)benzaldehyde (2.129). ALN-7-47. MeOH (74 mL) was added to a mixture of **2.141** (4.1 g, 22 mmol) and Na_2HPO_4 (6.2 g, 44 mmol). The heterogeneous reaction was placed in an oil bath preheated to 75 ˚C and heated under reflux for 2 h. The reaction was removed from the oil bath, cooled to room temperature, filtered through celite eluting with MeOH (50 mL), and the combined filtrates were concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (20 mL), H_2O (20 mL), and 1 M HCl (2 mL), and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (2 x 15 mL), and the combined organic layers were washed with brine (1 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography eluting with Hexanes:EtOAc (4:1) to furnish 3.7 g (90%) of **2.129** as an oil that solidified upon standing: mp 35-36 ˚C; ^{1}H NMR (400 MHz) δ 9.83 (s, 1 H), 7.64 (d, *J* = 2.0 Hz, 1 H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 6.40 (s, 1 H), 5.29 (s, 2 H), 3.54 (s, 3 H); ^{13}C NMR (100 MHz) δ 190.8, 152.2, 144.8, 129.8, 127.4, 115.4, 114.7, 95.7, 56.6; IR (CH_2Cl_2) 3356, 2961, 2832, 1681, 1591, 1512, 1291, 1154, 996 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_9H_{11}O_4]^+$ (M+H), 183.0657; found, 183.0659.

NMR Assignments. ^{1}H NMR (400 MHz) δ 9.83 (s, 1 H, C1-H), 7.64 (d, *J* = 2.0 Hz, 1 H, C6-H), 7.51 (dd, *J* = 8.4, 2.0 Hz, 1 H, C7-H), 7.07 (d, *J* = 8.4 Hz, 1 H, C3-H), 6.40 (s, 1 H, C5-OH), 5.29 (s, 2 H, C8-H), 3.54 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 190.8 (C1), 152.2 (C5), 144.8 (C4), 129.8 (C2), 127.4 (C7), 115.4 (C6), 114.7 (C3), 95.7 (C8), 56.6 (C9).



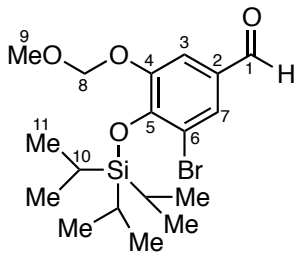
4-((3-Isopropyl-2,4-dimethylpentan-3-yl)oxy)-3-(methoxymethoxy) benzaldehyde (2.143). ALN-6-288. A mixture of **2.142** (0.10 g, 0.29 mmol) and Na_2HPO_4 (0.083 g, 0.58 mmol) in MeOH (1.5 mL) was placed in an oil bath preheated to 65 ˚C and stirred for 2 h. The reaction was cooled to ambient temperature, H_2O (2 mL), and the aqueous layer was washed with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine (1 x 5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude reside was purified by flash column chromatography eluting with Hexanes:EtOAc (5:1) to afford 0.085 g (86%) of **2.143** as a colorless oil; ^{1}H NMR (400 MHz) δ 9.84 (s, 1 H), 7.61 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 5.22 (s, 2 H), 3.51 (s, 3 H), 1.30 (hep, *J* = 7.2 Hz, 3 H), 1.12 (d, *J* = 7.2 Hz, 18 H); ^{13}C NMR (100 MHz) δ 190.8, 152.2, 148.8, 1305, 126.0, 120.5, 116.1, 94.9, 56.2, 17.7, 12.8; IR (CH_2Cl_2) 2946, 2868, 1696, 1593, 1508, 1290 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{31}O_3Si]^+$ (M+H), 323.2042; found, 323.2042.



3-Bromo-4-hydroxy-5-(methoxymethoxy)benzaldehyde (2.144). ALN-7-30. A solution of *N*-bromosuccinimide (0.21 g, 1.2 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 5 min *via* addition funnel to a solution of **2.129** (0.20 g, 1.1 mmol) and $HNEt_2$ (0.015 mL, 0.011 g, 0.11 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 2

h at room temperature, and then quenched with the addition of H_2O (10 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford 0.22 g (76%) of **2.144** as a beige powder (CH_2Cl_2/Hexanes): mp 126-127 ˚C (dec); ^{1}H NMR (400 MHz) δ 9.77 (s, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.58 (d, *J* = 1.6 Hz, 1 H), 6.86 (br s, 1 H), 5.29 (s, 2 H), 3.52 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.5, 149.3, 145.3, 130.0 x 2, 113.9, 109.2, 96.0, 56.8; IR (CH_2Cl_2) 3356, 2960, 2832, 1682, 1592, 1496, 1433, 1293, 1156, 1011 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_9H_9O_4Br]^{+\bullet}$ ($M^{+\bullet}$), 259.9684; found, 259.9681.

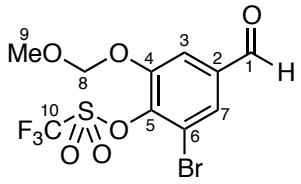
NMR Assignments. ^{1}H NMR (400 MHz) δ 9.77 (s, 1 H, C1-H), 7.72 (d, *J* = 1.6 Hz, 1 H, C7-H), 7.58 (d, *J* = 1.6 Hz, 1 H, C3-H), 6.86 (br s, 1 H, C5-OH), 5.29 (s, 2 H, C8-H), 3.52 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 189.5 (C1), 149.3 (C4), 145.3 (C5), 130.0 x 2 (C6+C7), 113.9 (C3), 109.2 (C2), 96.0 (C8), 56.8 (C9).



3-Bromo-5-(methoxymethoxy)-4-((triisopropylsilyl)oxy)benzaldehyde (2.145). ALN-7-22-2. Imidazole (0.27 g, 3.9 mmol) was added to a solution of **2.144** (0.51 g, 2.0 mmol) and TIPS-Cl (0.50 mL, 0.45 g, 2.3 mmol) in DMF (10 mL) at room temperature. The reaction was stirred for 4 h, and then quenched with chilled brine (10 mL) and H_2O (3 mL). The aqueous layer was washed with Et_2O (3 x 15 mL), and the combined organic layers were washed with H_2O (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered,

and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (6:1) to afford 0.80 g (98%) of **2.145** as a colorless oil; ^{1}H NMR (400 MHz) δ 9.78 (s, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.61 (d, *J* = 1.6 Hz, 1 H), 5.22 (s, 2 H), 3.49 (s, 3 H), 1.35 (hep, *J* = 7.6 Hz, 3 H), 1.12 (d, *J* = 7.6 Hz, 18 H); ^{13}C NMR (100 MHz) δ 189.7, 149.3, 149.2, 130.3, 129.3, 116.1, 113.6, 94.9, 56.5, 17.8, 14.1; IR (CH_2Cl_2) 2946, 2867, 1698, 1487, 1322, 1014 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{18}H_{30}O_4SiBr]^+$ (M+H), 417.1097; found, 417.1097.

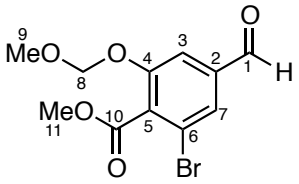
NMR Assignments. ^{1}H NMR (400 MHz) δ 9.78 (s, 1 H, C1-H), 7.72 (d, *J* = 1.6 Hz, 1 H, C7-H), 7.61 (d, *J* = 1.6 Hz, 1 H, C3-H), 5.22 (s, 2 H, C8-H), 3.49 (s, 3 H, C9-H), 1.35 (hep, *J* = 7.6 Hz, 3 H, C10-H), 1.12 (d, *J* = 7.6 Hz, 18 H, C11-H); ^{13}C NMR (100 MHz) δ 189.7 (C1), 149.3 (C4), 149.2 (C5), 130.3 (C2), 129.3 (C7), 116.1 (C6), 113.6 (C3), 94.9 (C8), 56.5 (C9), 17.8 (C11), 14.1 (C10).



2-Bromo-4-formyl-6-(methoxymethoxy)phenyl triflate (2.152). ALN-7-42. NaH (0.080 g, 2.0 mmol, 60% in oil) was added to a stirred solution of **2.144** (0.35 g, 1.3 mmol) and $PhN(Tf)_2$ (0.72 g, 2.0 mmol) in DMF (6.5 mL) at 0 ˚C. The reaction was stirred for 2.5 h, whereupon saturated aqueous NH_4Cl (10 mL) and H_2O (5 mL) were added. The aqueous layer was washed with Et_2O (3 x 15 mL), and the combined organic layers were washed with H_2O (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with Hexanes:EtOAc (15:1) to afford 0.50 g (94%) of **2.152** as a colorless oil; ^{1}H NMR (400 MHz) δ 9.93 (s, 1 H), 7.80 (d, *J* = 2.0 Hz, 1 H), 7.75 (d, *J* =

2.0 Hz, 1 H), 5.34 (s, 2 H), 3.54 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.1, 150.9, 141.1, 136.4, 127.7, 120.0, 117.5, 115.0, 95.5, 56.9; IR (CH_2Cl_2) 1709, 1592, 1427, 1216, 1134, 869 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{10}H_9O_6SBrF_3]^+$ (M+H), 392.9255; found, 392.9258.

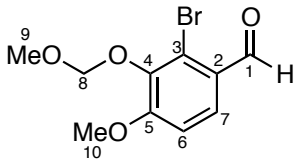
NMR Assignments. ^{1}H NMR (400 MHz) δ 9.93 (s, 1 H, C1-H), 7.80 (d, *J* = 2.0 Hz, 1 H, C7-H), 7.75 (d, *J* = 2.0 Hz, 1 H, C3-H), 5.34 (s, 2 H, C8-H), 3.54 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 189.1 (C1), 150.9 (C4), 141.1 (C5), 136.4 (C2), 127.7 (C7), 120.0 (C10), 117.5 (C6), 115.0 (C3), 95.5 (C8), 56.9 (C9).



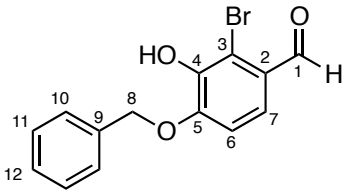
Methyl 2-bromo-4-formyl-6-(methoxymethoxy)benzoate (2.153). ALN-7-41. $Pd(OAc)_2$ (0.003 g, 0.013 mmol) and 1,3-bis(diphenylphosphino)propane (0.007 g, 0.017 mmol) were added to a solution of **2.152** (0.052 g, 0.13 mmol) in DMSO (1.3 mL). The mixture was purged with CO for 5 min at which time NEt_3 (0.13 mL, 0.094 g, 0.93 mmol) and MeOH (0.16 mL, 0.13 g, 4.0 mmol) were added. The solution was sparged with CO for an additional 5 min whereupon the reaction was placed in an oil bath preheated to 70 ˚C and stirred under CO (1 atm) for 5.5 h. The reaction was removed from the oil bath, cooled to room temperature, and diluted with H_2O (5 mL). The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organic layers were washed with H_2O (1 x 10 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (10:1) to afford 0.017 g (43%) of **2.153** as a colorless oil; ^{1}H NMR (400 MHz) δ 9.92 (s, 1 H), 7.71 (d, *J* = 1.6 Hz, 1 H), 7.61 (d, *J* = 1.6 Hz, 1 H), 5.25

(s, 2 H), 3.98 (s, 3 H), 3.47 (s, 3 H); ^{13}C NMR (100 MHz) δ 189.9, 165.6, 155.2, 138.5, 131.9, 127.2, 120.4, 113.5, 94.8, 56.5, 53.0; IR (CH_2Cl_2) 1740, 1704, 1566, 1275, 1006 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{11}H_{11}O_5Br]^+$ (M+H), 301.9790; found, 301.9793.

NMR Assignments. ^{1}H NMR (400 MHz) δ 9.92 (s, 1 H, C1-H), 7.71 (d, *J* = 1.6 Hz, 1 H, C7-H), 7.61 (d, *J* = 1.6 Hz, 1 H, C3-H), 5.25 (s, 2 H, C8-H), 3.98 (s, 3 H, C11-H), 3.47 (s, 3 H, C9-H); ^{13}C NMR (100 MHz) δ 189.9 (C1), 165.6 (C10), 155.2 (C4), 138.5 (C2), 131.9 (C7), 127.2 (C5), 120.4 (C6), 113.5 (C3), 94.8 (C8), 56.5 (C9), 53.0 (C11).

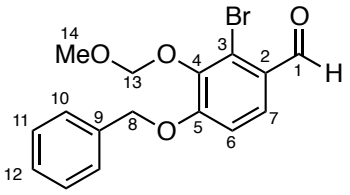


2-Bromo-4-methoxy-3-(methoxymethoxy)benzaldehyde (2.158). Prepared according to literature procedures.[277]

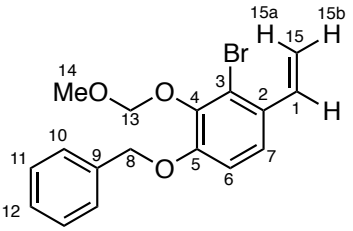


4-(Benzyloxy)-2-bromo-3-hydroxybenzaldehyde (2.154). ALN-7-74. A solution of NBS (0.40 g, 2.2 mmol) in CH_2Cl_2 (11 mL) was added dropwise over 15 min to a solution of **2.135** (0.49 g, 2.1 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred at ambient temperature for 1 h, H_2O (100 mL) was added, and the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from EtOH to afford 0.57 g (86%) of **2.154** as colorless

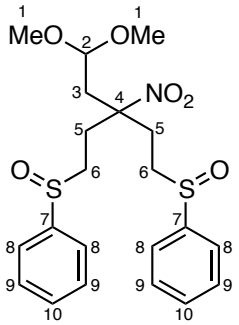
needles: mp 119-120 °C; ^{1}H NMR (400 MHz) δ 10.26 (s, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.42-7.39 (comp, 5 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.14 (s, 1 H), 5.23 (s, 2 H); ^{13}C NMR (100 MHz) δ 190.9, 150.7, 143.4, 134.8, 128.9 x 2, 127.9, 127.4, 122.5 , 113.0, 110.6, 71.6; IR (CH_2Cl_2) 3358, 2869, 1679, 1589, 1282, 1004 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{14}H_{12}O_3Br]^+$ (M+H), 306.9970; found, 306.9971.



4-(Benzyloxy)-2-bromo-3-(methoxymethoxy)benzaldehyde (2.155). ALN-7-67. *i*Pr$_2$NEt (1.8 mL, 1.3 g, 10 mmol) was added to a solution of **2.154** (0.80 g, 2.6 mmol) and MOM-Cl (0.40 ml, 0.42 g, 5.2 mmol) in CH_2Cl_2 at 0 °C. The solution was stirred at 0 °C for 1 h and then ambient temperature for 15 h. Saturated aqueous NH_4Cl (10 mL) and 1 M HCl (2 mL) were added, and the aqueous layers were washed with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with brine (1 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (10:1) to afford 0.62 g (66%) of **2.154** as a colorless oil that solidified upon standing: mp 52-53 °C; ^{1}H NMR (400 MHz) δ 10.28 (s, 1 H), 7.72 (d, *J* = 8.4 Hz, 1 H), 7.42-7.38 (comp, 5 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 5.21 (s, 2 H), 5.19 (s, 2 H), 3.60 (s, 3 H); ^{13}C NMR (100 MHz) δ 190.9, 157.2, 143.6, 135.2, 128.7, 128.5, 127.6, 127.5, 126.4, 123.2, 112.2, 98.8, 71.1, 58.1; IR (CH_2Cl_2) 2938, 1681, 1578, 1274, 1253, 912 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{16}H_{16}O_4Br]^+$ (M+H), 351.0232; found, 351.0232.

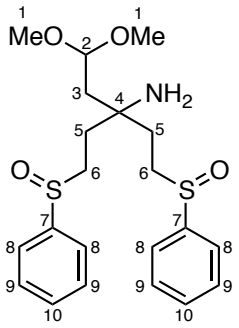


1-(Benzyloxy)-3-bromo-2-(methoxymethoxy)-4-vinylbenzene (2.156). ALN-7-72. NaH (0.056 g, 1.4 mmol) was added to a suspension of **2.155** (0.35 g, 1.0 mmol) and PPh_3CH_3 (0.43 g, 1.2 mmol) in THF (5 mL) at ambient temperature. The reaction was stirred for 15 h, diluted with Et_2O (10 mL), and washed with brine (10 mL). The layers were separated, and the aqueous layer was washed with Et_2O (2 x 15 mL). The combined organic layers were washed with H_2O (1 x 15 mL), brine (1 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (30:1) to afford 0.28 g (80%) of **2.156** as a colorless oil; ^{1}H NMR (400 MHz) δ 7.43-7.33 (comp, 5 H), 7.26 (m, 1 H), 7.02 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.52 (dd, *J* = 17.4, 1.2 Hz, 1 H), 5.26 (dd, *J* = 10.8, 1.2 Hz, 1 H), 5.20 (s, 2 H), 5.11 (s, 2 H), 3.61 (s, 3 H); ^{13}C NMR (100 MHz) δ 151.7, 143.6, 136.3, 135.6, 131.7, 128.6, 128.1, 127.4, 121.9, 119.6, 115.2, 113.1, 98.7, 71.1, 58.0; IR (CH_2Cl_2) 2926, 1588, 1483, 1288, 984, 913 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{17}O_3Br]^{+\bullet}$ ($M^{+\bullet}$), 348.0361; found, 348.0364.



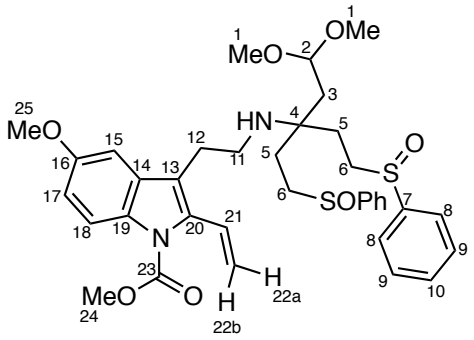
(3-(2,2-Dimethoxyethyl)-3-nitropentane-1,5-diyldisulfinyl)dibenzene (4.10). ALN-5-110. DBU (0.51 mL, 0.52 g, 3.4 mmol) was added dropwise over 1 min to a stirred solution of **4.9** (0.52 g, 3.4 mmol) and **4.8** (0.25 g, 1.7 mmol) in MeCN (6 mL) at room temperature. The reaction was stirred at room temperature for 30 h, and then CH_2Cl_2 (20 mL) and 1 M HCl (10 mL) were added. The aqueous layer was removed and washed with CH_2Cl_2 (2 x 15 mL), and the combined organic layers were washed with H_2O (1 x 15 mL), brine (1 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (1:1 to 1:4) to afford, as an inseparable mixture of diastereomers, 0.64 g (89%) of **4.10** as a viscous yellow oil; ^{1}H NMR (400 MHz) δ 7.60-7.51 (comp, 10 H), 4.23-4.17 (m, 1 H), 3.24-3.20 (comp, 6 H), 2.88-2.71 (comp, 2 H), 2.64-2.52 (comp, 2 H), 2.48-2.37 (comp, 2 H), 2.21-2.15 (comp, 2 H), 2.13-2.00 (comp, 2 H); ^{13}C NMR (100 MHz) δ 142.8, 142.7 x 2, 131.6, 131.5 x 2, 129.7, 124.3, 124.2 x 2, 101.4, 90.7, 90.6, 54.4, 54.3, 54.2, 50.2, 50.0, 49.9, 49.8, 39.3, 39.1, 39.0, 27.9, 27.7, 27.6, 27.5; IR (neat) 3457, 3058, 2938, 2834, 1543, 1444, 1364, 1193, 1124, 1085, 1045 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{21}H_{28}NO_6S_2]^+$ (M+H), 454.1358; found, 454.1362.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.60-7.51 (comp, 10 H, C8+C9+C10-H), 4.23-4.17 (m, 1 H, C2-H), 3.24-3.20 (comp, 6 H, C1-H), 2.88-2.71 (comp, 2 H, C6-H), 2.64-2.52 (comp, 2 H, C6-H), 2.48-2.37 (comp, 2 H, C5-H), 2.21-2.15 (comp, 2 H, C3-H), 2.13-2.00 (comp, 2 H, C5-H); ^{13}C NMR (100 MHz) δ 142.8 (C7), 142.7 x 2 (C7), 131.6 (C10), 131.5 x 2 (C10), 129.7 (C9), 124.3 (C8), 124.2 x 2 (C8), 101.4 (C2), 90.7 (C4), 90.6 (C4), 54.4 (C1), 54.3 (C1), 54.2 (C1), 50.2 (C6), 50.0 (C6), 49.9 (C6), 49.8 (C6), 39.3 (C3), 39.1 (C3), 39.0 (C3), 27.9 (C5), 27.7 (C5), 27.6 (C5), 27.5 (C5).



1,1-Dimethoxy-5-(phenylsulfinyl)-3-(2-(phenylsulfinyl)ethyl)pentan-3-amine (4.7). ALN-5-104. Zinc granules (1.8 g, 28 mmol) and NH_4Cl (1.8 g, 35 mmol) were added to a stirred solution of **4.10** (1.4 g, 3.1 mmol) in MeOH (30 mL) at room temperature. The mixture was heated under reflux for 2 h, cooled to room temperature, filtered through a plug of celite eluting with MeOH (100 mL) and CH_2Cl_2 (100 mL), and concentrated under reduced pressure to afford an off-white solid. The solid thus obtained was partitioned between CH_2Cl_2 (20 mL) and 1 M NaOH (10 mL). The pH of the aqueous layer was adjusted to pH 7 with 1 M HCl. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL), and the emulsion was filtered through a plug of celite. The filtrate was washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (10:1) to afford, as an inseparable mixture of diastereomers, 0.98 g (75%) of **4.7** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.59-7.47 (comp, 10 H), 4.38-4.34 (m, 1 H), 3.24-3.20 (comp, 6 H), 2.96-2.83 (comp, 2 H), 2.74-2.62 (comp, 2 H), 2.00 (br s, 2 H), 1.85-1.60 (comp, 2 H), 1.61-1.54 (comp, 4 H); ^{13}C NMR (125 MHz) δ 143.3, 143.2, 131.0 x 2, 129.2 x 2, 124.1, 124.0, 101.9, 53.3 x 2, 53.2 x 2, 52.6, 50.8, 41.4, 31.4; IR (CH_2Cl_2) 3449, 2933, 1433, 1039 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{21}H_{30}NO_4S_2]^+$ (M+H), 424.16108; found, 424.1608.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.59-7.47 (comp, 10 H, C8+C9+C10-H), 4.38-4.34 (m, 1 H, C2-H), 3.24-3.20 (comp, 6 H, C1-H), 2.96-2.83 (comp, 2 H, C6-H), 2.74-2.62 (comp, 2 H, C6-H), 2.00 (br s, 2 H, C4-NH_2), 1.85-1.60 (comp, 2 H, C3-H), 1.61-1.54 (comp, 4 H, C5-H); ^{13}C NMR (125 MHz) δ 143.3 (C7), 143.2 (C7), 131.0 x 2 (C10), 129.2 x 2 (C9), 124.1 (C8), 124.0 (C8), 101.9 (C2), 53.3 x 2 (C1), 53.2 x 2 (C1), 52.6 (C3), 50.8 (C6), 41.4 (C5), 31.4 (C4).



Methyl-3-(2-((1,1-dimethoxy-5-(phenylsulfinyl)-3-(2-(phenylsulfinyl)ethyl) pentan-3-yl)amino)ethyl)-5-methoxy-2-vinyl-1*H*-indole-1-carboxylate (4.14). ALN-5-157. A mixture of **4.6** (0.15 g, 0.54 mmol) and IBX (0.38 g, 1.3 mmol) in EtOAc (20 mL) was heated under reflux for 5 h. The mixture was cooled to room temperature, filtered through a plug of celite eluting with EtOAc, and the combined filtrate and washings were concentrated under reduced pressure. The crude aldehyde **4.13** was stirred with amine **4.7** (0.25 g, 0.59 mmol) in CH_2Cl_2 (15 mL) for 1 h at which time $NaB(OAc)_3H$ (0.16 g, 0.75 mmol) was added in one portion. The orange solution was stirred at room temperature for 13 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL), and the aqueous layer was washed with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (1 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column

chromatography eluting with CH_2Cl_2:MeOH (20:1) to afford, as an inseparable mixture of diastereomers, 0.36 g (97%) of **4.14** as a yellow oil; IR (CH_2Cl_2) 3456, 2953, 2833, 1732, 1610, 1477, 1442, 1123, 1042, 733 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{36}H_{45}N_2O_5S_2]^+$ (M+H), 681.26627; found, 681.2661.

Major Diastereomer. ^{1}H NMR (600 MHz) δ 7.95-7.93 (m, 1 H), 7.47-7.38 (comp, 10 H), 6.95 (br s, 1 H), 6.90-6.85 (comp, 2 H), 5.49 (dd, *J* = 17.7, 1.8 Hz, 1 H), 5.41 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.13-4.12 (m, 1 H), 3.97 (s, 3 H) 3.83 (s, 3 H), 3.08-3.03 (comp, 6 H), 2.78-2.76 (comp, 2 H), 2.69-2.54 (comp, 4 H), 2.51-2.43 (comp, 2 H), 1.70-1.65 (comp, 2 H), 1.46-1.39 (comp, 4 H).

Minor Diastereomer. ^{1}H NMR (600 MHz) δ 7.95-7.93 (m, 1 H), 7.47-7.38 (comp, 10 H), 6.95 (br s, 1 H), 6.90-6.85 (comp, 2 H), 5.48 (dd, *J* = 17.7, 1.8 Hz, 1 H), 5.40 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.13-4.12 (m, 1 H), 3.97 (s, 3 H) 3.83 (s, 3 H), 3.08-3.03 (comp, 6 H), 2.78-2.76 (comp, 2 H), 2.69-2.54 (comp, 4 H), 2.51-2.43 (comp, 2 H), 1.70-1.65 (comp, 2 H), 1.46-1.39 (comp, 4 H).

Mixture of diastereomers. ^{13}C NMR (150 MHz) δ 156.1 x 2, 152.2, 143.5, 143.4 x 2, 143.3, 136.2 x 3, 130.9 x 2, 130.8, 130.7 x 3, 130.0, 129.1 x 2, 128.4, 128.3, 123.9 x 2, 123.8 x 2, 118.1 x 2, 118.0, 116.4, 113.2, 101.7 x 3, 55.6, 55.0, 53.4, 53.1 x 2, 53.0 x 2, 50.5, 50.4, 50.3 x 2, 40.4, 40.3, 40.2, 38.2, 38.1, 27.3, 27.2, 27.1, 27.0, 25.4.

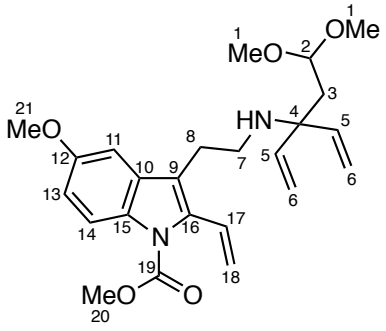
NMR Assignments.

Major Diastereomer. ^{1}H NMR (600 MHz) δ 7.95-7.93 (m, 1 H, C18-H), 7.47-7.38 (comp, 10 H, C8+C9+C10-H), 6.95 (br s, 1 H, C15-H), 6.90-6.85 (comp, 2 H, C17/C21-H), 5.49 (dd, *J* = 17.7, 1.8 Hz, 1 H, C22-Ha), 5.41 (dd, *J* = 11.4, 1.8 Hz, 1 H, C22-Hb), 4.13-4.12 (m, 1 H, C2-H), 3.97 (s, 3 H, C24-H) 3.83 (s, 3 H, C25-H), 3.08-3.03 (comp, 6 H, C1-H), 2.78-2.76 (comp, 2 H C11-H), 2.69-2.54 (comp, 4 H, C12/C6-H),

2.51-2.43 (comp, 2 H, C6-H), 1.70-1.65 (comp, 2 H, C3-H), 1.46-1.39 (comp, 4 H, C5-H).

Minor Diastereomer. ^{1}H NMR (600 MHz) δ 7.95-7.93 (m, 1 H, C18-H), 7.47-7.38 (comp, 10 H, C8+C9+C10-H), 6.95 (br s, 1 H, C15-H), 6.90-6.85 (comp, 2 H, C17/C21-H), 5.48 (dd, *J* = 17.7, 1.8 Hz, 1 H, C22-Ha), 5.40 (dd, *J* = 11.4, 1.8 Hz, 1 H, C22-Hb), 4.13-4.12 (m, 1 H, C2-H), 3.97 (s, 3 H, C24-H) 3.83 (s, 3 H, C25-H), 3.08-3.03 (comp, 6 H, C1-H), 2.78-2.76 (comp, 2 H, C11-H), 2.69-2.54 (comp, 4 H, C12/C6-H), 2.51-2.43 (comp, 2 H, C6-H), 1.70-1.65 (comp, 2 H, C3-H), 1.46-1.39 (comp, 4 H, C5-H).

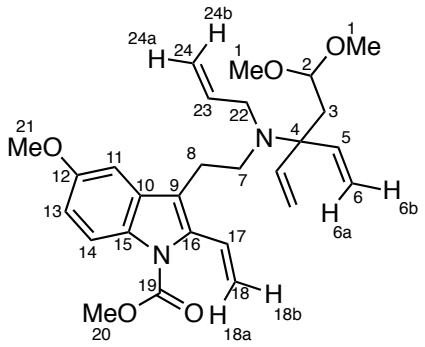
Mixture of diastereomers. ^{13}C NMR (150 MHz) δ 156.1 x 2 (C16), 152.2 (C23), 143.5 (C7), 143.4 x 2 (C7), 143.3 (C7), 136.2 x 3 (C20), 130.9 x 2 (C14), 130.8 (C14), 130.7 x 3 (C10), 130.0 (C19), 129.1 x 2 (C9), 128.4 (C21), 128.3 (C21), 123.9 x 2 (C8), 123.8 x 2 (C8), 118.1 x 2 (C13), 118.0 (C13), 116.4 (C17), 113.2 (C18), 101.7 x 3 (C15+C2), 55.6 (C25), 55.0 (C4), 53.4 (C24), 53.1 x 2 (C1), 53.0 x 2 (C1), 50.5 (C6), 50.4 (C6), 50.3 x 2 (C6), 40.4 (C12), 40.3 (C12), 40.2 (C12), 38.2 (C3), 38.1 (C3), 27.3 (C5), 27.2 (C5), 27.1 (C5), 27.0 (C5), 25.4 (C11).



Methyl-3-(2-((3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)ethyl)-5-methoxy-2-vinyl-1*H*-indole-1-carboxylate (4.15). ALN-5-165. A solution of **4.14**

(0.34 g, 0.50 mmol) and *i*Pr_2NEt (0.26 mL, 0.19 g, 1.5 mmol) in $PhCH_3$ (4 mL) was sparged with Ar for 4 min with stirring in a microwave vessel. The solution was heated at 150 ˚C for 3 h. After irradiation, the dark mixture was concentrated under reduced pressure and purified by flash column chromatography eluting with CH_2Cl_2:MeOH (20:1) to afford 0.14 g (67%) of **4.15** as a brown oil; ^{1}H NMR (500 MHz) δ 7.95 (d, *J* = 9.0 Hz, 1 H), 7.04 (br s, 1 H), 6.95 (dd, *J* = 17.7, 11.5 Hz, 1 H), 6.90 (dd, *J* = 9.1, 2.6 Hz), 5.78 (dd, *J* = 17.6, 11.1 Hz, 2 H), 5.51 (ddd, *J* = 21.1, 17.7, 1.8 Hz, 2 H), 5.13 (dd, *J* = 17.8, 11.0 Hz, 4 H), 4.45 (t, *J* = 5.1 Hz, 1 H), 4.00 (s, 3 H), 3.87 (s, 3 H), 3.22 (s, 6 H), 2.91 (t, *J* = 7.4 Hz, 2 H), 2.78 (t, *J* = 7.6 Hz, 2 H), 1.89 (d, *J* = 5.1 Hz, 2 H); ^{13}C NMR (125 MHz) δ 156.1, 152.4, 142.2, 135.9, 131.3, 130.0, 128.4, 118.8, 118.0, 116.3, 114.1, 113.2, 102.3, 101.9, 60.5, 55.7, 53.4, 52.6, 43.0, 39.9, 26.1; IR (CH_2Cl_2) 2954, 2832, 1734, 1610, 1477, 1441, 1251, 1121, 919 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{24}H_{33}N_2O_5]^+$ (M+H), 429.2389; found, 429.2378.

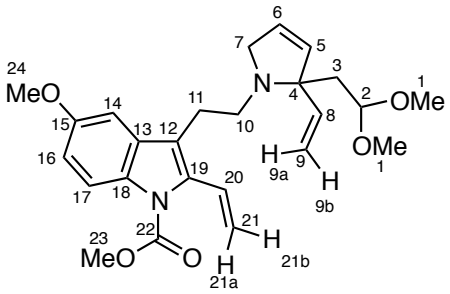
NMR Assignments. ^{1}H NMR (500 MHz) δ 7.95 (d, *J* = 9.0 Hz, 1 H, C14-H), 7.04 (br s, 1 H, C11-H), 6.95 (dd, *J* = 17.7, 11.5 Hz, 1 H, C17-H), 6.90 (dd, *J* = 9.1, 2.6 Hz, C13-H), 5.78 (dd, *J* = 17.6, 11.1 Hz, 2 H, C5-H), 5.51 (ddd, *J* = 21.1, 17.7, 1.8 Hz, 2 H, C18-H), 5.13 (dd, *J* = 17.8, 11.0 Hz, 4 H, C6-H), 4.45 (t, *J* = 5.1 Hz, 1 H, C2-H), 4.00 (s, 3 H, C20-H), 3.87 (s, 3 H, C21-H), 3.22 (s, 6 H, C1-H), 2.91 (t, *J* = 7.4 Hz, 2 H, C8-H), 2.78 (t, *J* = 7.6 Hz, 2 H, C7-H), 1.89 (d, *J* = 5.1 Hz, 2 H, C3-H); ^{13}C NMR (125 MHz) δ 156.1 (C12), 152.4 (C19), 142.2 (C5), 135.9 (C16), 131.3 (C10), 130.0 (C15), 128.4 (C17), 118.8 (C9), 118.0 (C18), 116.3 (C14), 114.1 (C6), 113.2 (C13), 102.3 (C2), 101.9 (C11), 60.5 (C4), 55.7 (C21), 53.4 (C20), 52.6 (C1), 43.0 (C7), 39.9 (C8), 26.1 (C3).



Methyl-3-(2-(allyl(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)ethyl)-5-methoxy-2-vinyl-1*H*-indole-1-carboxylate (4.5). ALN-5-191. K_2CO_3 (0.16 g, 1.2 mmol) was added to a stirred solution of **4.15** (0.10 g, 0.23 mmol) and **4.16** (0.20 mL, 0.28 g, 2.3 mmol) in MeCN (10 mL) in a resealable pressure tube. The solution was sparged with Ar for 4 min, the reaction was sealed, and the mixture was placed in an oil bath preheated to 110 ˚C. The mixture was stirred for 15 h at which time the reaction was cooled to room temperature. The reaction was filtered through celite, eluting with CH_2Cl_2 (25 mL), and the combined filtrate and washings were concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (5:1) to afford 0.082 g (75%) of **4.5** as a golden yellow oil; ^{1}H NMR (600 MHz) δ 7.94 (d, *J* = 9.0 Hz, 1 H), 6.99 (d, *J* = 2.6 Hz, 1 H), 6.93-6.90 (m, 1 H), 6.90-6.88 (m, 1 H), 6.02-5.96 (m, 1 H), 5.98 (dd, *J* = 18.3, 11.4 Hz, 2 H), 5.47 (s, 1 H), 5.44 (dd, *J* = 3.6, 1.8 Hz, 1 H), 5.28 (dd, *J* = 16.8, 1.8 Hz, 1 H), 5.21 (dd, *J* = 10.8, 1.2 Hz, 1 H), 5.11 (dd, *J* = 18.0, 1.2 Hz, 2 H), 5.11 (d, *J* = 2.4 Hz, 1 H), 4.72 (t, *J* = 4.4 Hz, 1 H), 3.99 (s, 3 H), 3.87 (s, 3 H), 3.31 (comp, 2 H), 3.30 (s, 6 H), 2.87-2.85 (comp, 2 H), 2.77-2.75 (comp, 2 H), 2.06 (d, *J* = 4.4 Hz, 2 H); ^{13}C NMR (150 MHz) δ 156.1, 152.4, 141.2, 139.6, 135.6, 131.3, 130.0, 128.6, 119.1, 117.7, 116.3, 115.1, 114.8, 113.1, 102.0, 101.9, 66.0, 55.7, 54.3, 53.4, 52.2, 51.3, 39.9, 26.8; IR (CH_2Cl_2) 3081, 2954, 2831,

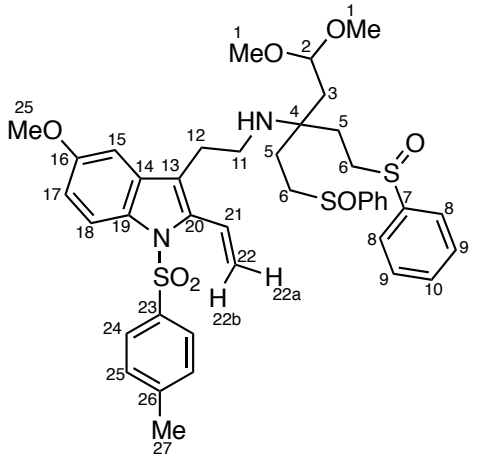
1735, 1611, 1441, 1251, 1118, 920 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{27}H_{37}N_2O_5]^+$ (M+H), 469.2702; found, 469.2701.

NMR Assignments. ^{1}H NMR (600 MHz) δ 7.94 (d, *J* = 9.0 Hz, 1 H, C14-H), 6.99 (d, *J* = 2.6 Hz, 1 H, C11-H), 6.93-6.90 (m, 1 H, C17-H), 6.90-6.88 (m, 1 H, C13-H), 6.02-5.96 (m, 1 H, C23-H), 5.98 (dd, *J* = 18.3, 11.4 Hz, 2 H, C5-H), 5.47 (s, 1 H, C18-Ha/Hb), 5.44 (dd, *J* = 3.6, 1.8 Hz, 1 H, C18-Ha/Hb), 5.28 (dd, *J* = 16.8, 1.8 Hz, 1 H, C24-Hb), 5.21 (dd, *J* = 10.8, 1.2 Hz, 1 H, C6-Hb), 5.11 (dd, *J* = 18.0, 1.2 Hz, 2 H, C6-Ha), 5.11 (d, *J* = 2.4 Hz, 1 H, C24-Ha), 4.72 (t, *J* = 4.4 Hz, 1 H, C2-H), 3.99 (s, 3 H, C20-H), 3.87 (s, 3 H, C21-H), 3.31 (comp, 2 H, C22-H), 3.30 (s, 6 H, C1-H), 2.87-2.85 (comp, 2 H, C8-H), 2.77-2.75 (comp, 2 H, C7-H), 2.06 (d, *J* = 4.4 Hz, 2 H, C3-H); ^{13}C NMR (150 MHz) δ 156.1 (C12), 152.4 (C19), 141.2 (C5), 139.6 (C23), 135.6 (C16), 131.3 (C10), 130.0 (C15), 128.6 (C17), 119.1 (C9), 117.7 (C18), 116.3 (C14), 115.1 (C24), 114.8 (C6), 113.1 (C13), 102.0 (C2), 101.9 (C11), 66.0 (C4), 55.7 (C21), 54.3 (C22), 53.4 (C20), 52.2 (C1), 51.3 (C7), 39.9 (C3), 26.8 (C8).



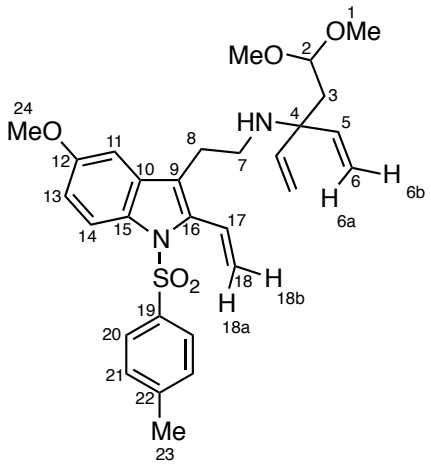
Methyl-3-(2-(2-(2,2-dimethoxyethyl)-2-vinyl-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-methoxy-2-vinyl-1*H*-indole-1-carboxylate (4.17). ALN-7-105. A solution of **4.5** (0.13 g, 0.28 mmol) in CH_2Cl_2 (2.8 mL) was degassed and backfilled with Ar 3x. Grubbs first generation catalyst (0.046 g, 0.056 mmol) was added, and the reaction was degassed and backfilled with Ar 3x. The reaction was placed in an oil bath preheated to

50 ˚C, heated under reflux for 3 h, cooled to ambient temperature, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (10:1) to afford 0.077 g (64%) of **4.17** as a green oil; ^{1}H NMR (400 MHz) δ 7.96 (d, *J* = 8.8 Hz, 1 H), 7.00-6.90 (comp, 3 H), 5.89 (m, 1 H), 5.74-5.67 (comp, 2 H), 5.49-5.44 (comp, 2 H), 5.07 (comp, 2 H), 4.52 (m, 1 H), 4.00 (s, 3 H), 3.94-3.88 (comp, 4 H), 3.40 (d, *J* = 14.0 Hz, 1 H), 3.27 (comp, 7 H), 2.95-2.85 (comp, 3 H), 2.62 (m, 1 H), 1.94-1.84 (comp, 3 H); ^{13}C NMR (100 MHz) δ 156.0, 152.3, 139.3, 135.5, 134.6, 131.2, 130.0, 128.9, 126.0, 119.1, 117.5, 116.4, 114.4, 113.0, 102.8, 101.7, 71.2, 57.9, 55.6, 53.4, 53.0, 52.6, 49.0, 38.7, 25.6; IR (CH_2Cl_2) 2926, 1733, 1610, 1477, 1440, 1367, 772 cm^{-1}; HRMS (CI) calculated for $[C_{25}H_{33}N_2O_5]^+$ (M+H), 441.2389; found, 441.2381.



1,1-Dimethoxy-*N*-(2-(5-methoxy-1-tosyl-2-vinyl-1*H*-indol-3-yl)ethyl)-5-(phenylsulfinyl)-3-(2-(phenylsulfinyl)ethyl)pentan-3-amine (4.22). ALN-5-221. A mixture of **4.20** (0.28 g, 1.0 mmol) and IBX (0.84 g, 3.0 mmol) in EtOAc (20 mL) was heated under reflux for 5 h. The mixture was cooled to room temperature, filtered through a plug of celite eluting with EtOAc, and the combined filtrate and washings were

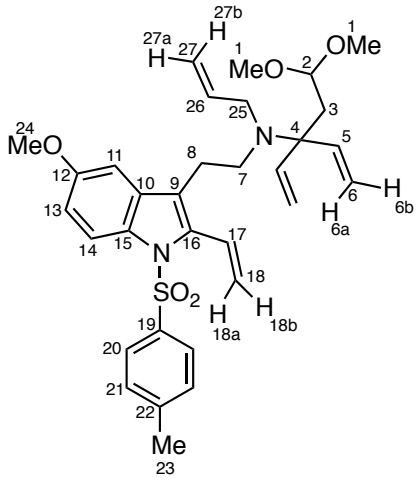
concentrated under reduced pressure. The crude aldehyde **4.21** was stirred with amine **4.7** (0.47 g, 1.1 mmol) in CH_2Cl_2 (20 mL) for 1 h at which time $NaB(OAc)_3H$ (0.30 g, 1.4 mmol) was added in one portion. The orange solution was stirred at room temperature for 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL), and the aqueous layer was washed with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (30:1) to afford, as an inseparable mixture of diastereomers, 0.50 g (64%) of **4.22** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.97 (m, 1 H), 7.36-7.30 (comp, 12 H), 6.96-6.71 (comp, 5 H), 5.52-5.40 (m, 1 H), 5.40-5.34 (m, 1 H), 3.97-3.92 (comp, 3 H), 3.66 (s, 3 H), 2.99-2.90 (comp, 6 H), 2.59-2.58 (comp, 2 H), 2.39-2.32 (comp, 4 H), 2.18-2.13 (comp, 2 H), 2.10-2.07 (comp, 3 H), 1.53-1.43 (comp, 3 H), 1.29-1.21 (comp, 4 H).



3-(2,2-Dimethoxyethyl)-*N*-(2-(5-methoxy-1-tosyl-2-vinyl-1*H*-indol-3-yl)ethyl) penta-1,4-dien-3-amine (4.23). ALN-5-224. A solution of **4.22** (0.084 g, 0.12 mmol) and *i*Pr_2NEt (0.056 mL, 0.042 g, 0.32 mmol) in $PhCH_3$ was sparged with Ar for 10 min, and then heated in a microwave oven at 150 ˚C for 3 h. The dark reaction mixture was

concentrated under reduced pressure and purified by flash column chromatography eluting with CH_2Cl_2:MeOH (20:1) to afford 0.050 g (89%) of **4.23** as a brown oil; ^{1}H NMR (400 MHz) δ 8.07 (d, *J* = 9.6 Hz, 1 H), 7.56 (d, *J* = 8.4 H, 2 H), 7.12-7.05 (comp, 3 H), 6.91-6.89 (comp, 2 H), 5.71-5.56 (comp, 4 H), 5.08 (d, *J* = 11.2 Hz, 2 H), 5.01 (d, *J* = 17.6 Hz, 2 H), 4.36 (t, *J* = 4.8 Hz, 1 H), 3.82 (s, 3 H), 3.15 (s, 6 H), 2.83 (app t, *J* = 6.8 H, 2 H), 2.66 (app t, *J* = 6.8 Hz, 2 H), 2.29 (s, 3 H), 1.82 (d, *J* = 4.4 Hz, 2 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 8.07 (d, *J* = 9.6 Hz, 1 H, C14-H), 7.56 (d, *J* = 8.4 H, 2 H, C20-H), 7.12-7.05 (comp, 3 H, C21+C17-H), 6.91-6.89 (comp, 2 H, C11+C13-H), 5.71-5.56 (comp, 4 H, C18a+C18b+C5-H), 5.08 (d, *J* = 11.2 Hz, 2 H, C6b-H), 5.01 (d, *J* = 17.6 Hz, 2 H, C6a-H), 4.36 (t, *J* = 4.8 Hz, 1 H, C2-H), 3.82 (s, 3 H, C24-H), 3.15 (s, 6 H, C1-H), 2.83 (app t, *J* = 6.8 H, 2 H, C7-H), 2.66 (app t, *J* = 6.8 Hz, 2 H, C8-H), 2.29 (s, 3 H, C23-H), 1.82 (d, *J* = 4.4 Hz, 2 H, C3-H).

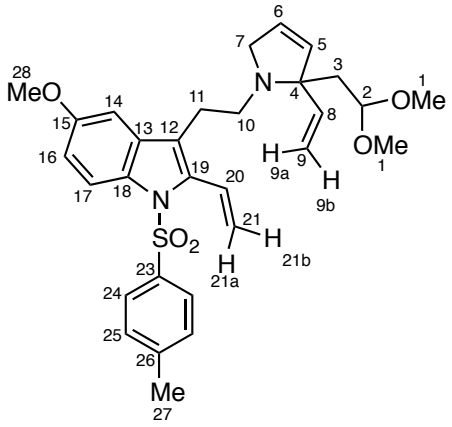


***N*-Allyl-3-(2,2-dimethoxyethyl)-*N*-(2-(5-methoxy-1-tosyl-2-vinyl-1*H*-indol-3-yl)ethyl)penta-1,4-dien-3-amine (4.24). ALN-6-227-2.** A mixture of **4.16** (0.14 mL, 0.20 g, 1.6 mmol), **4.23** (0.085 g, 0.16 mmol) and K_2CO_3 (0.11 g, 0.81 mmol) was stirred in MeCN (8.0 mL) in a resealable pressure tube. The mixture was sparged with Ar for 10

min, sealed, and then placed in an oil bath preheated to 105 ˚C. The reaction was stirred for 18 h, cooled to room temperature, and then filtered through celite eluting with CH_2Cl_2 (25 mL). The combined filtrate and washings were concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford 0.057 g (63%) of **4.24** as a yellow oil; ^{1}H NMR (500 MHz) δ 8.05 (dd, *J* = 8.5, 0.4 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.03 (dd, *J* = 17.7, 11.4 Hz, 1 H), 6.89-6.88 (comp, 2 H), 5.97-5.90 (m, 1 H), 5.91 (dd, *J* = 17.7, 11.0 Hz, 2 H), 5.54 (dd, *J* = 11.3, 1.6 Hz, 1 H), 5.43 (dd, *J* = 17.7, 1.6 Hz, 1 H), 5.22 (dd, *J* = 17.1, 1.9 Hz, 1 H), 5.18 (dd, *J* = 11.0, 1.1 Hz, 2 H), 5.08 (dd, *J* = 17.9, 1.1 Hz, 2 H), 5.06-5.04 (m, 1 H), 4.67 (t, *J* = 4.3 Hz, 1 H), 3.82 (s. 3 H), 3.27 (s, 3 H), 3.24 (d, *J* = 6.0 Hz, 2 H), 2.79-2.76 (comp, 2 H), 2.63-2.60 (comp, 2 H), 2.31 (s, 3 H), 2.02 (d, *J* = 4.4 Hz, 2 H); ^{13}C NMR (125 MHz) δ 156.7, 144.3, 141.2, 139.5, 136.0, 135.2, 132.4, 130.9, 129.4, 127.8, 126.7, 121.5, 119.5, 116.2, 115.2, 114.9, 113.6, 102.2, 102.0, 66.0, 55.6, 54.2, 52.2, 50.9, 39.9, 27.0, 21.5; IR (CH_2Cl_2) 3083, 2924, 1607, 1475, 1371, 1164, 666 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{32}H_{41}N_2O_5S]^+$ (M+H), 565.27307; found, 565.2735.

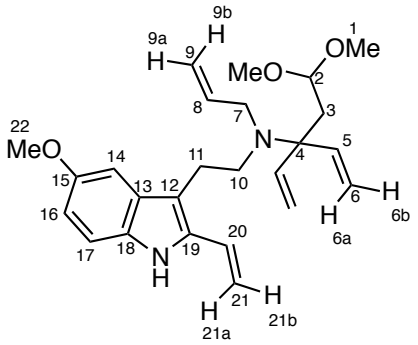
NMR Assignments. ^{1}H NMR (500 MH) δ 8.05 (dd, *J* = 8.5, 0.4 Hz, 1 H, C14-H), 7.55 (d, *J* = 8.4 Hz, 2 H, C20-H), 7.11 (d, *J* = 8.0 Hz, 2 H, C21-H), 7.03 (dd, *J* = 17.7, 11.4 Hz, 1 H, C17-H), 6.89-6.88 (comp, 2 H, C11/C13-H), 5.97-5.90 (m, 1 H, C26-H), 5.91 (dd, *J* = 17.7, 11.0 Hz, 2 H, C5-H), 5.54 (dd, *J* = 11.3, 1.6 Hz, 1 H, C18-Hb), 5.43 (dd, *J* = 17.7, 1.6 Hz, 1 H, C18-Ha), 5.22 (dd, *J* = 17.1, 1.9 Hz, 1 H, C27-Hb), 5.18 (dd, *J* = 11.0, 1.1 Hz, 2 H, C6-Hb), 5.08 (dd, *J* = 17.9, 1.1 Hz, 2 H, C6-Ha), 5.06-5.04 (m, 1 H, C27-Ha), 4.67 (t, *J* = 4.3 Hz, 1 H, C2-H), 3.82 (s, 3 H, C24-H), 3.27 (s, 3 H, C1-H), 3.24 (d, *J* = 6.0 Hz, 2 H, C25-H), 2.79-2.76 (comp, 2 H, C8-H), 2.63-2.60 (comp, 2 H, C7-H), 2.31 (s, 3 H, C23-H), 2.02 (d, *J* = 4.4 Hz, 2 H, C3-H); ^{13}C NMR (125 MHz) δ 156.7

(C12), 144.3 (C22), 141.2 (C5), 139.5 (C26), 136.0 (C16), 135.2 (C19), 132.4 (C10), 130.9 (C15), 129.4 (C21), 127.8 (C17), 126.7 (C20), 121.5 (C9), 119.5 (C18), 116.2 (C14), 115.2 (C27), 114.9 (C6), 113.6 (C13), 102.2 (C4), 102.0 (C11), 66.0 (C4), 55.6 (C24), 54.2 (C25), 52.2 (C1), 50.9 (C7), 39.9 (C3), 27.0 (C8), 21.5 (C23).



3-(2-(2-(2,2-Dimethoxyethyl)-2-vinyl-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-5-methoxy-1-tosyl-2-vinyl-1*H*-indole (4.25). ALN-6-23. A solution of **4.24** (0.010 g, 0.018 mmol) in C_7F_8 (1.8 mL) was sparged with Ar for 2 min. Grubbs-Hoveyda II (0.0010 g, 0.002 mmol) was added, and the reaction was sparged for an additional 2 min. Every 3 h, the reaction was cooled to ambient temperature and treated with additional catalyst (0.0010 g, 0.001 mmol) until the reaction was stirred for 9 h in total. The reaction was cooled to ambient temperature, concentrated under reduced pressure, and purified by flash column chromatography eluting with Hexanes:EtOAc (6:1). Analysis by LC-MS data indicated that **4.25** was formed in 86%; ^{1}H NMR (400 MHz) δ 8.10 (d, *J* = 9.2 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 7.16-7.14 (comp, 3 H), 7.02-6.93 (comp, 3 H), 6.70-s, 1 H), 5.21 (dd, *J* = 17.0, 10.4 Hz, 1 H), 6.13-6.08 (comp, 2 H), 5.47 (d, *J* = 11.2 Hz, 1 H), 5.29 (d, *J* = 17.6 Hz, 1 H), 4.92 (d, *J* = 11.2 Hz, 1 H), 4.77 (d, *J* = 18.0 Hz, 1

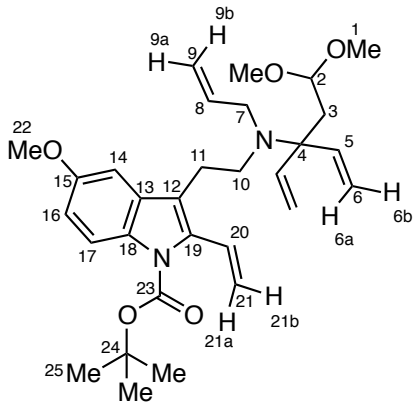
H), 4.27 (t, *J* = 4.4 Hz, 1 H), 4.08 (t, *J* = 6.8 Hz, 2 H), 3.79 (s, 3 H), 3.21 (s, 6 H), 2.98 (t, *J* = 6.0 Hz, 2 H), 2.60 (d, *J* = 5.6 Hz, 2 H), 2.34 (s, 3 H).



***N*-Allyl-3-(2,2-dimethoxyethyl)-*N*-(2-(5-methoxy-2-vinyl-1*H*-indol-3-yl)ethyl)penta-1,4-dien-3-amine (4.27). ALN-5-204.** LiOH•H_2O (0.034 g, 0.82 mmol) was added to a stirred solution of **4.5** (0.077 g, 0.16 mmol) in a solution of H_2O (1 mL) and THF (3 mL). The reaction was heated under reflux for 24 h, cooled to room temperature by removing from the oil bath, and diluted with H_2O (10 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 15 mL), and the combined organic layers were washed with brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 0.070 g (99%) of **4.27** as a yellow oil that required no further purification; ^{1}H NMR (400 MHz) δ 7.88 (br s, 1 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 6.97 (d, *J* = 2.0 Hz, 1 H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.77 (dd, *J* = 16.0, 9.6 Hz, 1 H), 6.03-6.00 (m, 1 H), 6.00 (dd, *J* = 17.8, 11.2 Hz, 2 H), 5.38-5.07 (comp, 8 H), 4.77 (t, *J* = 4.4 Hz, 1 H), 3.85 (s, 3 H), 3.31 (s, 6 H), 3.25 (d, *J* = 1.2 Hz, 2 H), 2.86-2.81 (comp, 2 H), 2.71-2.68 (comp, 2 H), 2.06 (d, *J* = 1.2 Hz, 2 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.88 (br s, 1 H, indole *N-H*), 7.16 (d, *J* = 8.4 Hz, 1 H, C17-H), 6.97 (d, *J* = 2.0 Hz, 1 H, C14-H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1 H, C16-H), 6.77 (dd, *J* = 16.0, 9.6 Hz, 1 H, C20-H), 6.03-6.00 (m, 1 H), 6.00 (dd, *J* = 17.8,

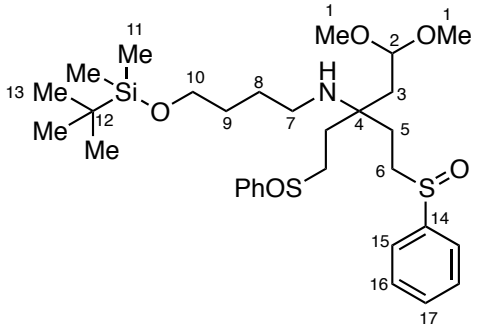
11.2 Hz, 2 H, C5-H), 5.38-5.07 (comp, 8 H, C21a+C21b+C6a+C6b+C9a+C9b-H), 4.77 (t, *J* = 4.4 Hz, 1 H, C2-H), 3.85 (s, 3 H, C22-H), 3.31 (s, 6 H, C1-H), 3.25 (d, *J* = 1.2 Hz, 2 H, C7-H), 2.86-2.81 (comp, 2 H, C10-H), 2.71-2.68 (comp, 2 H, C11-H), 2.06 (d, *J* = 1.2 Hz, 2 H, C3-H).



***tert*-Butyl-3-(2-(allyl(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)ethyl)-5-methoxy-2-vinyl-1*H*-indole-1-carboxylate (4.28). ALN-5-239.** A solution of **4.27** (0.047 g, 0.11 mmol), DMAP (0.001 g, 0.0034 mmol), and Boc_2O (0.035 g, 0.16 mmol) in MeCN (1.1 mL) was stirred at ambient temperature for 24 h. The reaction was diluted with H_2O (10 mL) and brine (5 mL). The aqueous layer was washed with CH_2Cl_2 (4 x 20 mL), and the combined organic layers were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with Hexanes:EtOAc (6:1) to afford 0.092 g (77%) of **4.28** as a yellow oil; ^{1}H NMR (600 MHz) δ 7.94 (d, *J* = 9.0 Hz, 1 H), 6.98 (d, *J* = 2.6 Hz, 1 H), 6.91-6.86 (comp, 2 H), 6.03-5.96 (m, 1 H), 5.97 (dd, *J* = 17.8, 10.9 Hz, 2 H), 5.43-5.40 (comp, 2 H), 5.28 (dd, *J* = 16.3, 1.9 Hz, 1 H), 5.20 (dd, *J* = 10.9, 1.2 Hz, 2 H), 5.12-5.11 (m, 1 H), 5.11 (dd, *J* = 17.7, 1.2 Hz, 2 H), 4.72 (t, *J* = 4.4 Hz, 1 H), 3.86 (s, 3 H), 3.31 (comp, 2 H), 3.30 (s, 6 H), 2.87-2.84 (comp, 2 H), 2.77-2.74 (comp, 2 H), 2.06

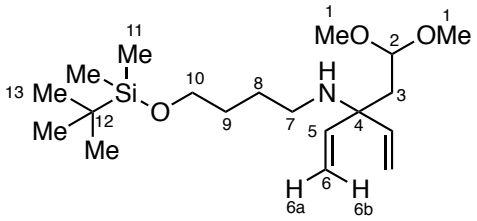
(d, J = 4.4 Hz, 2 H), 1.65 (s, 9 H); ^{13}C NMR (150 MHz) δ 155.8, 150.5, 141.3, 139.7, 135.8, 131.2, 130.2, 129.1, 118.4, 117.1, 116.3, 115.1, 114.8, 112.9, 102.0, 101.8, 83.6, 66.1, 55.7, 54.2, 52.2, 51.4, 40.0, 28.3, 26.8; IR (CH_2Cl_2) 3081, 2933, 1728, 1611, 1478, 1370, 1331, 1119 cm^{-1}; HRMS (CI) m/z calculated for $[C_{30}H_{43}N_2O_5]^+$ (M+H), 511.3172; found, 511.3171.

NMR Assignments. ^{1}H NMR (600 MHz) δ 7.94 (d, J = 9.0 Hz, 1 H, C17-H), 6.98 (d, J = 2.6 Hz, 1 H, C14-H), 6.91-6.86 (comp, 2 H, C16/C20-H), 6.03-5.96 (m, 1 H, C8-H), 5.97 (dd, J = 17.8, 10.9 Hz, 2 H, C5-H), 5.43-5.40 (comp, 2 H, C21a/C21b-H), 5.28 (dd, J = 16.3, 1.9 Hz, 1 H, C9b-H), 5.20 (dd, J = 10.9, 1.2 Hz, 2 H, C6b-H), 5.12-5.11 (m, 1 H, C9a-H), 5.11 (dd, J = 17.7, 1.2 Hz, 2 H, C6a-H), 4.72 (t, J = 4.4 Hz, 1 H, C2-H), 3.86 (s, 3 H, C22-H), 3.31 (comp, 2 H, C7-H), 3.30 (s, 6 H, C1-H), 2.87-2.84 (comp, 2 H, C11-H), 2.77-2.74 (comp, 2 H, C10-H), 2.06 (d, J = 4.4 Hz, 2 H, C3-H), 1.65 (s, 9 H, C25-H); ^{13}C NMR (150 MHz) δ 155.8 (C15), 150.5 (C23), 141.3 (C5), 139.7 (C8), 135.8 (C19), 131.2 (C13), 130.2 (C12), 129.1 (C20), 118.4 (C18), 117.1 (C21), 116.3 (C17), 115.1 (C9), 114.8 (C6), 112.9 (C16), 102.0 (C2), 101.8 (C14), 83.6 (C24), 66.1 (C4), 55.7 (C22), 54.2 (C7), 52.2 (C1), 51.4 (C10), 40.0 (C3), 28.3 (C25), 26.8 (C11).



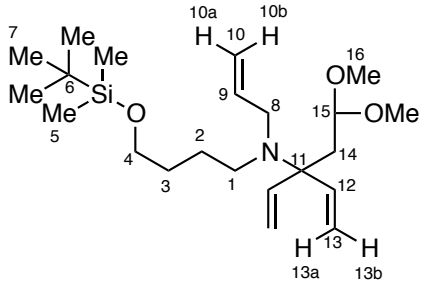
***N*-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-1,1-dimethoxy-5-(phenylsulfinyl)-3-(2-(phenylsulfinyl)ethyl)pentan-3-amine (4.33). ALN-6-48.** Aldehyde **4.34** (0.33 g, 1.6 mmol) was added to a mixture of **4.7** (0.97 g, 2.3 mmol) and 3 Å molecular sieves (0.20 g) in CH_2Cl_2 (16 mL). The imine was formed for 18 h at which time $NaB(OAc)_3H$ (0.45 g, 2.1 mmol) was added. The reaction was stirred 3.5 h, saturated aqueous $NaHCO_3$ (20 mL) was added, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (25:1) to afford 0.99 g (99%) of **4.33** as an inseparable mixture of diastereomers as a yellow oil; ^{1}H NMR (400 MHz) δ 7.59-7.48 (comp, 10 H), 4.24 (br s, 1 H), 3.5 (t, *J* = 6.4 Hz, 2 H), 3.21-3.16 (comp, 6 H), 2.86-2.78 (comp, 2 H), 2.65-2.58 (comp, 2 H), 2.22-2.15 (comp, 2 H), 1.71-1.34 (comp, 12 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (150 MHz) δ 143.6, 130.9, 129.2, 124.1, 101.8, 63.0, 55.0, 53.2, 53.1, 50.6, 50.5, 50.4, 40.3, 38.4, 30.7, 27.3, 27.1, 26.0, 18.4, -5.3; IR (CH_2Cl_2) 3466, 2931, 1472, 1444, 1253, 1087, 1044, 836 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{31}H_{52}NO_5SiS_2]^+$ (M+H), 610.3056; found, 610.3063.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.59-7.48 (comp, 10 H, C15/C16/C17-H), 4.24 (br s, 1 H C2-H), 3.5 (t, *J* = 6.4 Hz, 2 H, C10-H), 3.21-3.16 (comp, 6 H, C1-H), 2.86-2.78 (comp, 2 H, C6-H), 2.65-2.58 (comp, 2 H, C6-H), 2.22-2.15 (comp, 2 H, C7-H), 1.72 (comp, 2 H, C5-H), 1.54-1.44 (comp, 6 H, C5/C8/C9-H), 1.38-1.33 (comp, 2 H, C3-H), 0.89 (s, 9 H, C13-H), 0.04 (s, 6 H, C11-H); ^{13}C NMR (150 MHz) δ 143.6 (C14), 130.9 (C17), 129.2 (C16), 124.1 (C15), 101.8 (C2), 63.0 (C10), 55.0 (C7), 53.2 (C1), 53.1 (C1), 50.6 (C6), 50.5 (C6), 50.4 (C6), 40.3 (C7), 38.4 (C3), 30.7 (C5/C8/C9), 27.3 (C5/C8/C9), 27.1 (C5/C8/C9), 26.0 (C13), 18.4 (C12), -5.3 (C11).



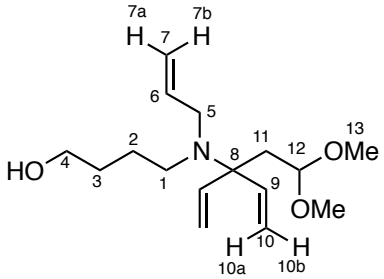
***N*-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-3-(2,2-dimethoxyethyl)penta-1,4-dien-3-amine (4.34). ALN-6-56.** A solution of **4.33** (0.37 g, 0.61 mmol) and *i*Pr_2NEt (0.32 mL, 0.24 g, 1.8 mmol) in $PhCH_3$ was sparged with Ar for 4 min. The reaction was then heated in a microwave oven at 150 ˚C for 3.5 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (30:1) to afford 0.20 g (91%) of **4.34** as a red-orange oil; ^{1}H NMR (400 MHz) δ 5.79 (dd, *J* = 17.6, 11.2 Hz, 2 H), 5.18-5.10 (comp, 4 H), 4.51 (t, *J* = 4.8 Hz, 1 H), 3.60 (t, *J* = 6.0 Hz, 2 H), 3.29 (s, 3 H), 2.45 (t, *J* = 6.8 Hz, 2 H), 1.89 (d, *J* = 4.8 Hz, 2 H), 1.56-1.45 (comp, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (150 MHz) δ 142.5, 113.9, 102.4, 63.1, 60.4, 52.7, 42.4, 40.3, 30.7, 27.2, 26.0, 18.4, -5.3; IR (CH_2Cl_2) 2931, 1471, 1254, 1120, 1100, 837 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{19}H_{39}NO_3Si]^+$ (M+H), 357.2699; found 357.2691.

NMR Assignments. ^{1}H NMR (400 MHz) δ 5.79 (dd, *J* = 17.6, 11.2 Hz, 2 H, C5-H), 5.18-5.10 (comp, 4 H, C6+C14-H), 4.51 (t, *J* = 4.8 Hz, 1 H, C2-H), 3.60 (t, *J* = 6.0 Hz, 2 H, C10-H), 3.29 (s, 3 H, C1-H), 2.45 (t, *J* = 6.8 Hz, 2 H, C7-H), 1.89 (d, *J* = 4.8 Hz, 2 H, C3-H), 1.56-1.45 (comp, 4 H, C8+C9-H), 0.88 (s, 9 H, C13-H), 0.03 (s, 6 H, C11-H); ^{13}C NMR (150 MHz) δ 142.5 (C5), 113.9 (C6), 102.4 (C2), 63.1 (C10), 60.4 (C4), 52.7 (C1), 42.4 (C7), 40.3 (C3), 30.7 (C9), 27.2 (C8), 26.0 (C13), 18.4 (C12), -5.3 (C11).



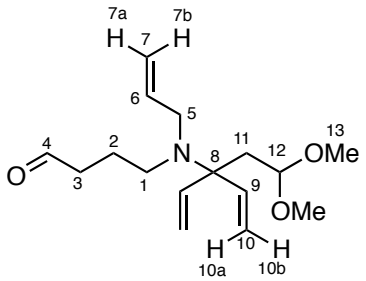
***N*-Allyl-*N*-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3-(2,2-dimethoxyethyl) penta-1,4-dien-3-amine (4.35). ALN-6-304.** A mixture of **4.16** (0.41 mL, 0.58 g, 4.8 mmol), **4.34** (0.17 g, 0.48 mmol) and K_2CO_3 (0.26 g, 1.9 mmol) was stirred in MeCN (15 mL) in a resealable pressure tube. The mixture was sparged with Ar for 4 min, and then placed in an oil bath preheated to 100 ˚C. The reaction was stirred for 18 h, cooled to room temperature, filtered through celite eluting with CH_2Cl_2 (50 mL), and the combined filtrate and washings were concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (30:1) to afford 0.18 g (95%) of **4.35** as a colorless oil; ^{1}H NMR (400 MHz) δ 5.91 (dd, *J* = 17.8, 10.8 Hz, 2 H), 5.86-5.84 (m, 1 H), 5.17 (d, *J* = 12.0 Hz, 2 H), 5.14 (m, 1 H), 5.08 (d, *J* = 17.6 Hz, 2 H), 4.96 (d, *J* = 9.6 Hz, 1 H), 4.64 (t, *J* = 4.4 Hz, 1 H), 3.56 (app t, *J* = 6.0 Hz, 2 H), 3.27 (s, 6 H), 3.13 (d, *J* = 6.4 Hz, 2 H), 2.48 (app t, *J* = 6.0 Hz, 2 H), 1.97 (d, *J* = 4.4 Hz, 2 H), 1.44-1.42 (comp, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 5.91 (dd, *J* = 17.8, 10.8 Hz, 2 H, C12-H), 5.86-5.84 (m, 1 H, C9-H), 5.17 (d, *J* = 12.0 Hz, 2 H, C13b-H), 5.14 (m, 1 H, C10b-H), 5.08 (d, *J* = 17.6 Hz, 2 H, C13a-H), 4.96 (d, *J* = 9.6 Hz, 1 H, C10a-H), 4.64 (t, *J* = 4.4 Hz, 1 H, C15-H), 3.56 (app t, *J* = 6.0 Hz, 2 H, C4-H), 3.27 (s, 6 H, C16-H), 3.13 (d, *J* = 6.4 Hz, 2 H, C1-H), 2.48 (app t, *J* = 6.0 Hz, 2 H, C8-H), 1.97 (d, *J* = 4.4 Hz, 2 H, C14-H), 1.44-1.42 (comp, 4 H, C2+C3-H), 0.88 (s, 9 H, C7-H), 0.03 (s, 6 H, C5-H).



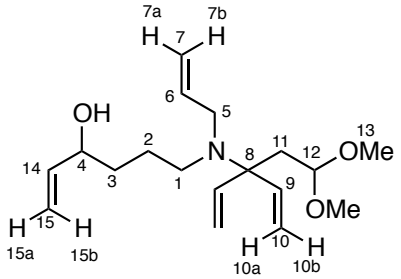
4-(Allyl(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)butan-1-ol (4.36). ALN-6-291. TBAF•3(H_2O) (0.13 g, 0.43 mmol) was added to a solution of **4.35** (0.069 g, 0.17 mmol) in THF (1.7 mL) at room temperature. After stirring for 3.5 h, saturated aqueous NH_4Cl (10 mL) was added, and the aqueous layer was washed with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (2:1) to afford 0.043 g (88%) of **4.36** as a colorless oil; ^{1}H NMR (400 MHz) δ 5.97-5.87 (comp, 3 H), 5.23 (d, *J* = 10.8 Hz, 2 H), 5.12 (d, *J* = 16.8 Hz, 1 H), 5.11 (d, *J* = 18.4 Hz, 2 H), 5.00 (d, *J* = 9.6 Hz, 1 H), 4.56 (t, *J* = 4.4 Hz, 1 H), 3.60 (t, *J* = 5.6 Hz, 2 H), 3.26 (s, 6 H), 3.17 (d, *J* = 6.0 Hz, 2 H), 2.53 (t, *J* = 6.4 Hz, 2 H), 2.02 (comp, 2 H), 1.62-1.54 (comp, 4 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 5.97-5.87 (comp, 3 H, C9+C6-H), 5.23 (d, *J* = 10.8 Hz, 2 H, C10b-H), 5.12 (d, *J* = 16.8 Hz, 1 H, C7b-H), 5.11 (d, *J* = 18.4 Hz, 2 H, C10a-H), 5.00 (d, *J* = 9.6 Hz, 1 H, C7a-H), 4.56 (t, *J* = 4.4 Hz, 1 H, C12-H), 3.60 (t, *J* = 5.6 Hz, 2 H, C4-H), 3.26 (s, 6 H, C13-H), 3.17 (d, *J* = 6.0 Hz, 2 H, C8-H), 2.53 (t, *J* = 6.4 Hz, 2 H, C1-H), 2.02 (comp, 2 H, C11-H), 1.62-1.54 (comp, 4 H, C2+C3-H).



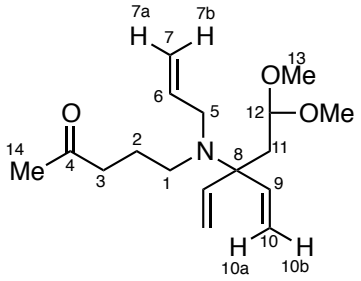
4-(Allyl(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)butanal (4.37). **ALN-6-22.** IBX (0.27 g, 0.96 mmol) was added to a solution of **4.36** (0.14 g, 0.49 mmol) in DMSO (5 mL) at room temperature. The reaction was stirred for 4.5 h whereupon saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer was washed with Et_2O (3 x 15 mL), and the combined organic layers were washed with brine (1 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (4:1) to afford 0.11 g (79%) of **4.37** as a colorless oil; ^{1}H NMR (400 MHz) δ 9.74 (s, 1 H), 5.89 (dd, *J* = 17.4, 10.8 Hz, 2 H), 5.86-5.81 (m, 1 H), 5.20 (d, *J* = 10.8 Hz, 2 H), 5.16 (d, *J* = 18.0 Hz, 1 H), 5.08 (d, *J* = 18.4 Hz, 2 H), 4.99 (d, *J* = 9.6 H, 1 H), 4.61 (t, *J* = 4.4 Hz, 1 H), 3.27 (s, 6 H), 3.14 (d, *J* = 6.0 Hz, 2 H), 2.52 (t, *J* = 14.4 Hz, 2 H), 2.40 (t, *J* = 14.4 Hz, 2 H), 1.98 (d, *J* = 4.4 Hz, 2 H), 1.72 (p, *J* = 7.2 Hz, 2 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 9.74 (s, 1 H, C4-H), 5.89 (dd, *J* = 17.4, 10.8 Hz, 2 H, C9-H), 5.86-5.81 (m, 1 H, C6-H), 5.20 (d, *J* = 10.8 Hz, 2 H, C10b-H), 5.16 (d, *J* = 18.0 Hz, 1 H, C7b-H), 5.08 (d, *J* = 18.4 Hz, 2 H, C10a-H), 4.99 (d, *J* = 9.6 H, 1 H, C7a-H), 4.61 (t, *J* = 4.4 Hz, 1 H, C12-H), 3.27 (s, 6 H, C13-H), 3.14 (d, *J* = 6.0 Hz, 2 H, C5-H), 2.52 (t, *J* = 14.4 Hz, 2 H, C3-H), 2.40 (t, *J* = 14.4 Hz, 2 H, C1-H), 1.98 (d, *J* = 4.4 Hz, 2 H, C11-H), 1.72 (p, *J* = 7.2 Hz, 2 H, C2-H).



6-(Allyl(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)hex-1-en-3-ol

(4.39). ALN-6-24. A solution of vinyl magnesium bromide (0.74 mL, 0.48 mmol, 0.64 M in THF) was added to a solution of **4.38** (0.067 g, 0.24 mmol) in THF (2.4 mL) at 0 ˚C. The solution was stirred for 2 h, whereupon saturated aqueous NH_4Cl (10 mL) was added. The aqueous layer was washed with Et_2O (3 x 15 mL), and the combined organic layers were washed with brine (1 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford 0.049 g (66%) of **4.39** as a colorless oil; ^{1}H NMR (400 MHz) δ 5.95-5.81 (comp, 4 H), 5.27-5.17 (comp, 3 H), 5.13-5.07 (comp, 4 H), 5.01-4.99 (m, 1 H), 4.57-4.56 (m, 1 H), 4.12-4.04 (m, 1 H), 3.26 (s, 6 H), 3.17 (comp, 2 H), 2.52 (comp, 2 H), 2.07-1.99 (comp, 2 H), 1.58-1.51 (comp, 4 H).

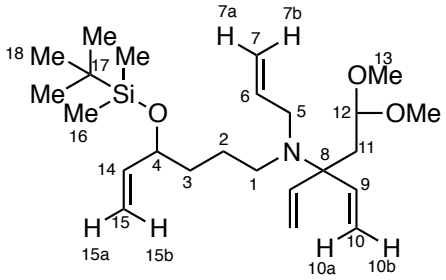


5-(Allyl(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)amino)pentan-2-one

(4.44). ALN-6-31. Ti(O*i*Pr)$_4$ (0.0040 mL, 0.0040 g, 0.014 mmol) was added to a solution of **4.39** (0.014 g, 0.045 mmol) in CH_2Cl_2 (4.5 mL). The solution was stirred for

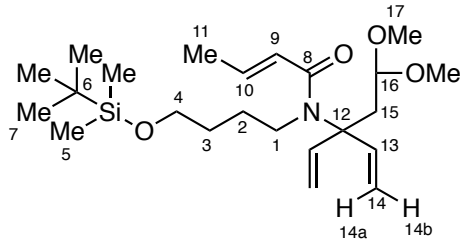
3 min at which time Grubbs first generation catalyst (0.007 g, 0.009 mmol) was added. The reaction was degassed and backfilled with Ar 3x and then heated in a microwave oven at 50 ˚C for 3 h. The reaction was cooled to room temperature, concentrated under reduced pressure, and purified by flash column chromatography eluting with Hexanes:EtOAc (5:1) to afford 0.0020 g (20%) of **4.44** as a brown oil; ^{1}H NMR (400 MHz) δ 5.89 (dd, *J* = 17.4, 10.8 Hz, 2 H), 5.84-5.81 (m, 1 H), 5.19 (d, *J* = 10.8 Hz, 2 H), 5.15-5.14 (m, 1 H), 5.07 (d, *J* = 17.4 Hz, 2 H), 4.98 (d, *J* = 10.4 Hz, 1 H), 4.62 (t, *J* = 4.4 Hz, 1 H), 3.27 (s, 6 H), 3.14 (d, *J* = 5.6 Hz, 2 H), 2.48 (app t, *J* = 7.2 Hz, 2 H), 2.37 (t, *J* = 6.8 Hz, 2 H), 2.12 (s, 3 H), 1.98 (d, *J* = 4.4 Hz, 2 H), 1.66 (p, *J* = 7.6 Hz, 2 H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 5.89 (dd, *J* = 17.4, 10.8 Hz, 2 H, C9-H), 5.84-5.81 (m, 1 H, C6-H), 5.19 (d, *J* = 10.8 Hz, 2 H, C10b-H), 5.15-5.14 (m, 1 H, C7b-H), 5.07 (d, *J* = 17.4 Hz, 2 H, C10a-H), 4.98 (d, *J* = 10.4 Hz, 1 H, C7a-H), 4.62 (t, *J* = 4.4 Hz, 1 H, C12-H), 3.27 (s, 6 H, C13-H), 3.14 (d, *J* = 5.6 Hz, 2 H, C5-H), 2.48 (app t, *J* = 7.2 Hz, 2 H, C3-H), 2.37 (t, *J* = 6.8 Hz, 2 H, C1-H), 2.12 (s, 3 H, C14-H), 1.98 (d, *J* = 4.4 Hz, 2 H, C11-H), 1.66 (p, *J* = 7.6 Hz, 2 H, C2-H).



***N*-Allyl-4-((*tert*-butyldimethylsilyl)oxy)-*N*-(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)hex-5-en-1-amine (4.50). ALN-6-34.** Imidazole (0.0030 g, 0.047 mmol) was added to a solution of **4.39** (0.012 g, 0.039 mmol) and TBS-Cl (0.0090 g, 0.058 mmol) in DMF (2 mL) at room temperature. The reaction was stirred for 5 h, H_2O (10 mL) was

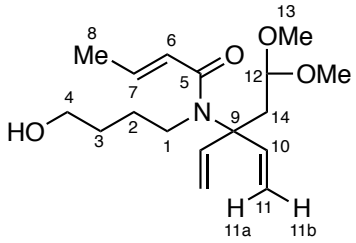
added, and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (6:1) to afford 0.011 g (69%) of **4.50** as a colorless oil; ^{1}H NMR (400 MHz) δ 5.97-5.73 (comp, 4 H), 5.19-4.95 (comp, 8 H), 4.64 (t, *J* = 4.4 Hz, 1 H), 4.04 (d, *J* = 6.0 Hz, 2 H), 3.27 (s, 6 H), 3.17-3.12 (comp, 2 H), 2.48-1.97 (comp, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H).



(*E*)-*N*-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-*N*-(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)but-2-enamide (4.54). ALN-6-53. Crotonoyl chloride (0.022 mL, 0.024 g, 0.23 mmol) was added to a solution of **4.34** (0.074 g, 0.21 mmol) and *i*Pr_2NEt (0.054 mL, 0.040 g, 0.31 mmol) in CH_2Cl_2 (2.1 mL) at 0 ˚C. The reaction was stirred for 2 h, whereupon H_2O (15 mL) was added. The aqueous layer was washed with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (30:1) to afford 0.085 g (97%) of **4.54** as an orange oil; ^{1}H NMR (400 MHz) δ 6.89-6.84 (m, 1 H), 6.22 (d, *J* = 12.8 Hz, 1 H), 6.11 (dd, *J* = 17.2, 10.4 Hz, 2 H), 5.16 (d, *J* = 10.4 Hz, 2 H), 5.07 (d, *J* = 17.6 Hz, 2 H), 4.45 (t, *J* = 5.2 Hz, 1 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 3.34-3.27 (comp,

8 H), 2.49 (d, *J* = 4.8 Hz, 2 H), 1.85 (d, *J* = 6.8 Hz, 3 H), 1.69-1.63 (comp, 2 H), 1.49-1.44 (comp, 2 H), 0.90 (s, 9 H), 0.04 (s, 6 H).

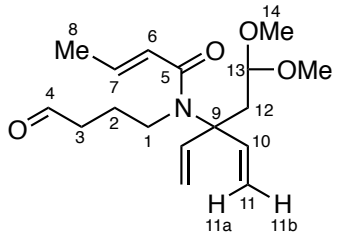
NMR Assignments. ^{1}H NMR (400 MHz) δ 6.89-6.84 (m, 1 H, C10-H), 6.22 (d, *J* = 12.8 Hz, 1 H, C9-H), 6.11 (dd, *J* = 17.2, 10.4 Hz, 2 H, C13-H), 5.16 (d, *J* = 10.4 Hz, 2 H, C14b-H), 5.07 (d, *J* = 17.6 Hz, 2 H, C14a-H), 4.45 (t, *J* = 5.2 Hz, 1 H, C16-H), 3.62 (t, *J* = 6.0 Hz, 2 H, C4-H), 3.34-3.27 (comp, 8 H, C17+C1-H), 2.49 (d, *J* = 4.8 Hz, 2 H, C15-H), 1.85 (d, *J* = 6.8 Hz, 3 H, C11-H), 1.69-1.63 (comp, 2 H, C2-H), 1.49-1.44 (comp, 2 H, C3-H), 0.90 (s, 9 H, C7-H), 0.04 (s, 6 H, C5-H).



(*E*)-*N*-(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)-*N*-(4-hydroxybutyl)but-2-enamide (4.55). ALN-6-54. TBAF (0.074, 0.23 mmol) was added to a solution of **4.54** (0.050 g, 0.12 mmol) in THF (1.5 mL) at 0 ˚C. The reaction was stirred for 4 h, whereupon saturated aqueous NH_4Cl (10 mL) was added. The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting with Hexanes:EtOAc (1:1) to afford 0.032 g (89%) of **4.55** as a colorless oil; ^{1}H NMR (400 MHz) δ 6.88-6.82 (m, 1 H), 6.22 (d, *J* = 13.2 Hz, 1 H), 6.10 (dd, *J* = 17.4, 10.4 Hz, 2 H), 5.19 (d, *J* = 10.4 Hz, 2 H), 5.08 (d, *J* = 17.4 Hz, 2 H), 4.45 (t, *J* = 5.2 Hz, 1 H), 3.67 (t, *J* = 6.4 Hz, 2 H), 3.37-3.33 (comp, 2 H), 3.27 (s, 6 H), 2.45 (d, *J* = 5.2 Hz, 2 H), 1.85 (d, *J* = 5.2 Hz, 3 H), 1.71-

1.65 (comp, 2 H), 1.55-1.50 (comp, 2 H); ^{13}C NMR (100 MHz) δ 167.4, 140.9, 140.2, 124.4, 113.9, 102.3, 65.6, 61.6, 52.6, 46.3, 38.9, 29.5, 27.7, 18.0; IR (CH_2Cl_2) 3434, 2937, 1660, 1612, 1407, 1122, 1068 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{17}H_{30}NO_4]^+$ (M+H), 312.2175; found, 312.2179.

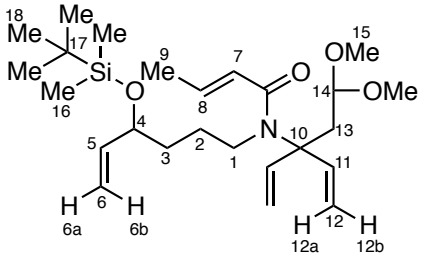
NMR Assignments. ^{1}H NMR (400 MHz) δ 6.88-6.82 (m, 1 H, C7-H), 6.22 (d, *J* = 13.2 Hz, 1 H, C6-H), 6.10 (dd, *J* = 17.4, 10.4 Hz, 2 H, C10-H), 5.19 (d, *J* = 10.4 Hz, 2 H, C11b-H), 5.08 (d, *J* = 17.4 Hz, 2 H, C11a-H), 4.45 (t, *J* = 5.2 Hz, 1 H, C12-H), 3.67 (t, *J* = 6.4 Hz, 2 H, C4-H), 3.37-3.33 (comp, 2 H, C1-H), 3.27 (s, 6 H, C13-H), 2.45 (d, *J* = 5.2 Hz, 2 H, C14-H), 1.85 (d, *J* = 5.2 Hz, 3 H, C8-H), 1.71-1.65 (comp, 2 H, C3-H), 1.55-1.50 (comp, 2 H, C2-H).



(*E*)-*N*-(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)-*N*-(4-oxobutyl)but-2-enamide (4.56). ALN-6-57. IBX (0.047 g, 0.17 mmol) was added to a solution of **4.55** (0.026 g, 0.083 mmol) in DMSO (2 mL) at ambient temperature. The reaction was stirred for 8 h, whereupon saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer was washed with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (1:1) to afford 0.017 g (65%) of **4.56** as a colorless oil; ^{1}H NMR (400 MHz) δ 9.78 (s, 1 H), 6.91-6.82 (m, 1 H), 6.33 (d, *J* = 13.2 Hz, 1 H), 6.11 (dd, *J* = 17.4,

10.4 Hz, 2 H), 5.21 (d, *J* = 10.4 Hz, 2 H), 5.06 (d, *J* = 17.4 Hz, 2 H), 4.43 (t, *J* = 5.2 Hz, 1 H), 3.37-3.33 (comp, 2 H), 3.27 (s, 6 H), 2.46-2.40 (comp, 4 H), 1.94-1.78 (comp, 7 H).

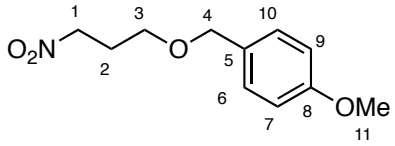
NMR Assignments. ^{1}H NMR (400 MHz) δ 9.78 (s, 1 H, C4-H), 6.91-6.82 (m, 1 H, C7-H), 6.33 (d, *J* = 13.2 Hz, 1 H, C6-H), 6.11 (dd, *J* = 17.4, 10.4 Hz, 2 H, C10-H), 5.21 (d, *J* = 10.4 Hz, 2 H, C11b-H), 5.06 (d, *J* = 17.4 Hz, 2 H, C11a-H), 4.43 (t, *J* = 5.2 Hz, 1 H, C13-H), 3.37-3.33 (comp, 2 H, C1-H), 3.27 (s, 6 H, C14-H), 2.46-2.40 (comp, 4 H, C12+C3-H), 1.94-1.78 (comp, 7 H, C2+C3+C8-H).



(*E*)-*N*-(4-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-1-yl)-*N*-(3-(2,2-dimethoxyethyl)penta-1,4-dien-3-yl)but-2-enamide (4.58). ALN-6-63. A solution of vinyl magnesium bromide (0.13 mL, 0.082 mmol, 0.64 M in THF) was added to a solution of **4.56** (0.017 g, 0.055 mmol) in THF (3 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 1 h and then ambient temperature for 1 h. Saturated aqueous NH_4Cl (10 mL) was added, and the aqueous layer was washed with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was dissolved in DMF (1 mL) and stirred with TBS-Cl (0.0040 g, 0.027 mmol) and imidazole (0.0010 g, 0.021 mmol) at room temperature for 5 h. H_2O (10 mL) was added, and the aqueous layer was washed with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was

purified by flash column chromatography eluting with Hexanes:EtOAc (3:1) to afford 0.004 g (50% over two steps) of **4.58** as a colorless oil; ^{1}H NMR (400 MHz) δ 6.89-6.84 (m, 1 H), 6.19 (d, *J* = 13.2 Hz, 1 H), 6.13-6.05 (comp, 2 H), 5.83-5.74 (m, 1 H), 5.21-5.45 (comp, 6 H), 4.44 (t, *J* = 5.2 Hz, 1 H), 4.14-4.11 (m, 1 H), 3.32-3.25 (comp, 8 H), 2.49 (app t, *J* = 4.0 Hz, 2 H), 1.85 (d, *J* = 6.8 Hz, 3 H), 1.63-1.57 (comp, 2 H), 1.45-1.40 (comp, 2 H), 0.89 (s, 9 H), 0.03 (s, 6 H).

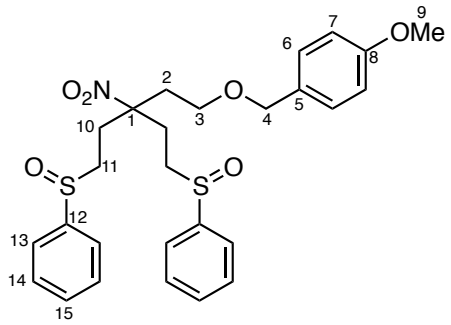
NMR Assignments. ^{1}H NMR (400 MHz) δ 6.89-6.84 (m, 1 H, C8-H), 6.19 (d, *J* = 13.2 Hz, 1 H, C7-H), 6.13-6.05 (comp, 2 H, C11-H), 5.83-5.74 (m, 1 H, C5-H), 5.21-5.45 (comp, 6 H, C6+C12-H), 4.44 (t, *J* = 5.2 Hz, 1 H, C14-H), 4.14-4.11 (m, 1 H, C4-H), 3.32-3.25 (comp, 8 H, C1+C15-H), 2.49 (app t, *J* = 4.0 Hz, 2 H, C13-H), 1.85 (d, *J* = 6.8 Hz, 3 H, C9-H), 1.63-1.57 (comp, 2 H, C3-H), 1.45-1.40 (comp, 2 H, C2-H), 0.89 (s, 9 H, C18-H), 0.03 (s, 6 H, C16-H).



1-Methoxy-4-((3-nitropropoxy)methyl)benzene (4.74). ALN-6-79. Camphorsulfonic acid (0.38 g, 1.7 mmol) was added to a solution of **4.72** (1.7 g, 17 mmol) and **4.73** (5.2 mL, 7.0 g, 25 mmol) in a solution of cyclohexane (10 mL) and CH_2Cl_2 (10 mL) at 0 ˚C. The mixture was stirred at 0 ˚C for 1 h, the ice bath was removed, and the reaction was warmed to room temperature. Reaction was filtered after 4 h, and the filter cake was rinsed with petroleum ether (30 mL). The filtrate was diluted with CH_2Cl_2 (30 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 x 30 mL), brine (1 x 30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with

Hexanes:EtOAc (5:1) to afford 3.60 g (98%) of **4.74** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.23 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 4.48 (t, *J* = 6.8 Hz, 2 H), 4.42 (s, 2 H), 3.79 (s, 3 H), 3.52 (t, *J* = 5.8 Hz, 2 H), 2.25 (p, *J* = 5.8 Hz, 2 H); ^{13}C NMR (100 MHz) δ 159.1, 129.7, 129.1, 113.6, 72.6, 72.6, 65.7, 55.0, 27.4; IR (CH_2Cl_2) 2866, 1714, 1612, 1552, 1513, 1462, 1097 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{11}H_{15}NO_4]^{+\bullet}$ ($M^{\bullet+}$), 225.1001; found, 225.1000.

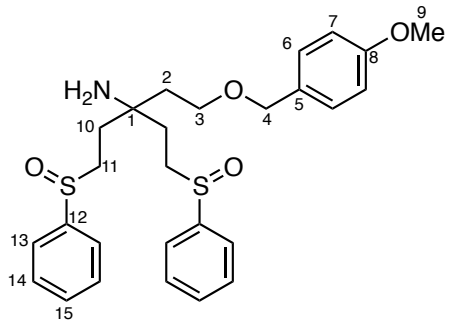
NMR Assignments. ^{1}H NMR (400 MHz) δ 7.23 (d, *J* = 8.8 Hz, 2 H, C6+C10-H), 6.88 (d, *J* = 8.8 Hz, 2 H, C7+C9-H), 4.48 (t, *J* = 6.8 Hz, 2 H, C1-H), 4.42 (s, 2 H, C4-H), 3.79 (s, 3 H, C11-H), 3.52 (t, *J* = 5.8 Hz, 2 H, C3-H), 2.25 (p, *J* = 5.8 Hz, 2 H, C2-H); ^{13}C NMR (100 MHz) δ 159.1 (C8), 129.7 (C5), 129.1 (C6+C10), 113.6 (C7+C9), 72.6 (C4), 72.6 (C1), 65.7 (C3), 55.0 (C11), 27.4 (C2).



(3-(2-((4-Methoxybenzyl)oxy)ethyl)-3-nitropentane-1,5-diyldisulfinyl)dibenzene (4.75). ALN-6-81. DBU (3.2 mL, 3.2 g, 21 mmol) was added to a solution of **4.74** (2.4 g, 11 mmol) and **4.9** (2.8 mL, 3.2 g, 21 mmol) in MeCN (40 mL) at ambient temperature. The reaction was stirred for 6 h, CH_2Cl_2 (50 mL) was added, and the organic phase was washed with 1 M aqueous HCl (40 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$), filtered,

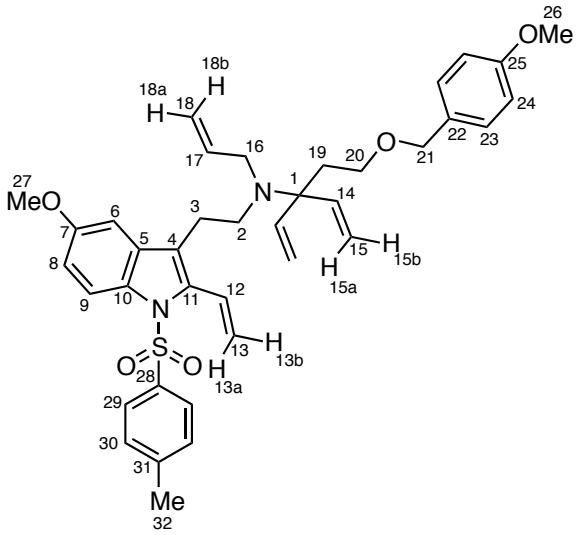
and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (1:1 to 1:6) to afford 4.8 g (86%) of **4.75** as mixture of diastereomers as a yellow oil; ^{1}H NMR (400 MHz) δ 7.51-7.45 (comp, 10 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 4.30-4.25 (comp, 2 H), 3.80 (s, 3 H), 3.38-3.34 (comp, 2 H), 2.83-2.72 (comp, 2 H), 2.62-2.49 (comp, 2 H), 2.48-2.36 (comp, 2 H), 2.21-2.15 (comp, 2 H), 2.15-2.04 (comp, 2 H); ^{13}C NMR (125 MHz) δ 159.4, 142.8, 142.7, 142.6 x 2, 131.3, 131.2 x 2, 129.5, 129.4 x 3, 129.3, 124.0 x 2, 123.9, 113.9, 91.7 x 2, 91.6, 73.0, 64.6 x 2, 64.5, 55.3, 50.5, 50.2, 50.1 x 2, 35.7, 35.6, 35.4, 28.1, 27.9, 27.8, 27.7; IR (CH_2Cl_2) 2934, 1540, 1247, 1043, 748 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{27}H_{31}NNaO_6S_2]^+$ (M+Na), 552.14850; found, 552.14834.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.51-7.45 (comp, 10 H, C13+C14+C15-H), 7.17 (d, *J* = 8.4 Hz, 2 H, C6-H), 6.88 (d, *J* = 8.4 Hz, 2 H, C7-H), 4.30-4.25 (comp, 2 H, C4-H), 3.80 (s, 3 H, C9-H), 3.38-3.34 (comp, 2 H, C3-H), 2.83-2.72 (comp, 2 H, C11-H), 2.62-2.49 (comp, 2 H, C11-H), 2.48-2.36 (comp, 2 H, C10-H), 2.21-2.15 (comp, 2 H, C2-H), 2.15-2.04 (comp, 2 H, C10-H); ^{13}C NMR (125 MHz) δ 159.4 (C8), 142.8 (C12), 142.7 (C12), 142.6 x 2 (C12), 131.3 (C15), 131.2 x 2 (C15), 129.5 (C5/C6/C14), 129.4 x 3 (C5/C6/C14), 129.3 (C5/C6/C14), 124.0 x 2 (C13), 123.9 (C13), 113.9 (C7), 91.7 x 2 (C1), 91.6 (C1), 73.0 (C4), 64.6 x 2 (C3), 64.5 (C3), 55.3 (C9), 50.5 (C11), 50.2 (C11), 50.1 x 2 (C11), 35.7 (C2), 35.6 (C2), 35.4 (C2), 28.1 (C10), 27.9 (C10), 27.8 (C10), 27.7 (C10).



1-((4-Methoxybenzyl)oxy)-5-(phenylsulfinyl)-3-(2(phenylsulfinyl)ethyl) pentan-3-amine (4.71). ALN-6-94. Zinc granules (0.65 g, 9.9 mmol) were added to a mixture of **4.75** (0.57 g, 1.1 mmol) and NH_4Cl (0.65 g, 12 mmol) in MeOH (25 mL). The mixture was heated in a 60 ˚C oil bath for 40 min and then cooled to room temperature. The mixture was filtered through a celite plug eluting with MeOH (50 mL) and then CH_2Cl_2 (50 mL). The combined filtrate and washings were concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The emulsion was filtered through a plug of celite, eluting with CH_2Cl_2 (40 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (40:1) to afford 0.39 g (72%) of **4.71** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.55-7.46 (comp, 10 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 4.30 (s, 2 H), 3.79 (s, 3 H), 3.44-3.41 (comp, 2 H), 2.93-2.84 (comp, 2 H), 2.72-2.63 (comp, 2 H), 1.84-1.77 (comp, 2 H), 1.65-1.60 (comp, 6 H); IR (CH_2Cl_2) 3366, 2933, 1612, 1513, 1444, 1248, 1087, 1037, 746 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{27}H_{34}NO_4S_2]^+$ (M+H), 500.19238; found, 500.19228.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.55-7.46 (comp, 10 H, C13+C14+C15-H), 7.18 (d, *J* = 8.4 Hz, 2 H, C6-H), 6.87 (d, *J* = 8.4 Hz, 2 H, C7-H), 4.30 (s, 2 H, C4-H), 3.79 (s, 3 H, C9-H), 3.44-3.41 (comp, 2 H, C3-H), 2.93-2.84 (comp, 2 H, C11-H), 2.72-2.63 (comp, 2 H, C11-H), 1.84-1.77 (comp, 2 H, C1-NH_2), 1.65-1.60 (comp, 6 H, C2+C10-H).

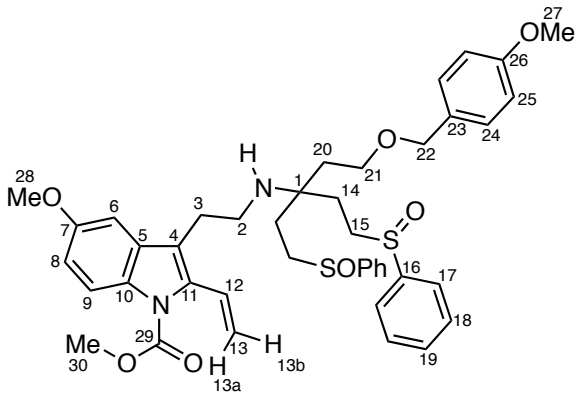


***N*-Allyl-*N*-(2-(5-methoxy-1-tosyl-2-vinyl-1*H*-indol-3-yl)ethyl)-3-(2-((4-methoxybenzyl)oxy)ethyl)penta-1,4-dien-3-amine (4.78). ALN-6-99.** A mixture of **4.77** (0.10 g, 0.17 mmol), **4.16** (0.14 mL, 0.20 g, 1.7 mmol) and K_2CO_3 (0.11 g, 0.83 mmol) in MeCN (10 mL) in a pressure tube was sparged with Ar for 10 min. The mixture was sealed, placed in an oil bath preheated to 115 ˚C, and stirred for 15 h. The reaction was removed from the heating bath, cooled to room temperature, filtered through celite eluting with CH_2Cl_2 (30 mL), and the combined filtrate and washings were concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with Hexanes:EtOAc (10:1) to afford 0.079 g (72%) of **4.78** as a yellow oil; ^{1}H NMR (500 MHz) δ 8.05 (d, *J* = 9.0 Hz, 1 H), 7.55 (d, *J* = 8.5 Hz, 2 H),

7.23 (d, *J* = 8.5 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 7.03 (dd, *J* = 17.7, 11.4 Hz, 1 H), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1 H) 6.85 (d, *J* = 8.7 Hz, 2 H), 6.83 (d, *J* = 2.5 Hz, 1 H), 5.93-5.86 (m, 1 H), 5.83 (dd, *J* = 17.7, 10.9 Hz, 2 H), 5.53 (dd, *J* = 11.4, 1.7 Hz, 1 H), 5.43 (dd, *J* = 17.7, 1.7 Hz, 1 H), 5.18 (dd, *J* = 17.2, 1.8 Hz, 1 H), 5.15 (dd, *J* = 10.9, 1.1 Hz, 2 H), 5.07 (dd, *J* = 17.7, 1.1 Hz, 2 H), 5.03 (dd, *J* = 10.1, 1.8 Hz, 1 H), 4.39 (s, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.55 (app t, *J* = 7.9 Hz, 2 H), 3.20 (d, *J* = 6.1 Hz, 2 H), 2.76-2.73 (comp, 2 H), 2.61-2.57 (comp, 2 H), 2.30 (s, 3 H), 2.03 (app t, *J* = 7.9 Hz, 2 H); ^{13}C NMR (125 MHz) δ 159.2, 156.6, 144.3, 141.1, 139.4, 136.0, 135.2, 132.3, 130.8, 130.6, 129.4, 129.2, 127.8, 126.7, 121.6, 119.5, 116.1, 115.2, 115.1, 113.8, 113.5, 102.2, 72.7, 66.7, 66.2, 55.6, 55.3, 54.1, 50.7, 36.2, 27.0, 21.5; IR (CH_2Cl_2) 2931, 1610, 1513, 1474, 1371, 1163, 666 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{38}H_{45}N_2O_5S]^+$ (M+H), 641.3049; found, 641.3045.

NMR Assignments. ^{1}H NMR (500 MHz) δ 8.05 (d, *J* = 9.0 Hz, 1 H, C9-H), 7.55 (d, *J* = 8.5 Hz, 2 H, C29-H), 7.23 (d, *J* = 8.5 Hz, 2 H, C24-H), 7.10 (d, *J* = 8.3 Hz, 2 H, C30-H), 7.03 (dd, *J* = 17.7, 11.4 Hz, 1 H, C12-H), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1 H, C8-H) 6.85 (d, *J* = 8.7 Hz, 2 H, C23-H), 6.83 (d, *J* = 2.5 Hz, 1 H, C6-H), 5.93-5.86 (m, 1 H, C17-H), 5.83 (dd, *J* = 17.7, 10.9 Hz, 2 H, C14-H), 5.53 (dd, *J* = 11.4, 1.7 Hz, 1 H, C13b-H), 5.43 (dd, *J* = 17.7, 1.7 Hz, 1 H, C13a-H), 5.18 (dd, *J* = 17.2, 1.8 Hz, 1 H, C18a-H), 5.15 (dd, *J* = 10.9, 1.1 Hz, 2 H, C15b-H), 5.07 (dd, *J* = 17.7, 1.1 Hz, 2 H, C15a-H), 5.03 (dd, *J* = 10.1, 1.8 Hz, 1 H, C18b-H), 4.39 (s, 2 H, C21-H), 3.79 (s, 3 H, C26-H), 3.78 (s, 3 H, C27-H), 3.55 (app t, *J* = 7.9 Hz, 2 H, C20-H), 3.20 (d, *J* = 6.1 Hz, 2 H, C16-H), 2.76-2.73 (comp, 2 H, C3-H), 2.61-2.57 (comp, 2 H, C2-H), 2.30 (s, 3 H, C32-H), 2.3 (app t, *J* = 7.9 Hz, 2 H, C19-H); ^{13}C NMR (125 MHz) δ 159.2 (C25), 156.6 (C7), 144.3 (C28), 141.1 (C14), 139.4 (C17), 136.0 (C11), 135.2 (C31), 132.3 (C5), 130.8 (C10), 130.6 (C22), 129.4 (C30), 129.2 (C24), 127.8 (C12), 126.7 (C29), 121.6 (C4), 119.5

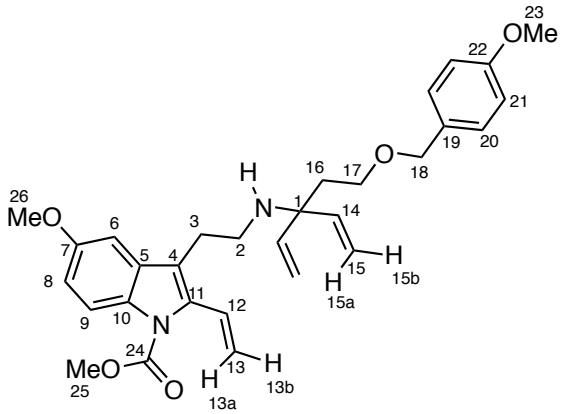
(C13), 116.1 (C9), 115.2 (C18), 115.1 (C15), 113.8 (C23), 113.5 (C8), 102.2 (C6), 72.7 (C21), 66.7 (C20), 66.2 (C1), 55.6 (C27), 55.3 (C26), 54.1 (C16), 50.7 (C2), 36.2 (C19), 27.0 (C3), 21.5 (C32).



Methyl-5-methoxy-3-(2-((1-((4-methoxybenzyl)oxy)-5-(phenylsulfinyl)-3-(2-(phenylsulfinyl)ethyl)pentan-3-yl)amino)ethyl)-2-vinyl-1*H*-indole-1-carboxylate (4.81). ALN-6-119. A mixture of IBX (1.2 g, 4.4 mmol) and **4.6** (0.40 g, 1.5 mmol) in EtOAc (15 mL) was heated under reflux for 2 h. The mixture was cooled to room temperature, filtered through a celite pad eluting with EtOAc (25 mL), and the combined filtrate and washings were concentrated under reduced pressure. The crude aldehyde was stirred with **4.71** (0.87 g, 1.7 mmol) for 1 h whereupon $NaB(OAc)_3H$ (0.46 g, 2.2 mmol) was added. The solution was stirred for 20 h at which time saturated aqueous $NaHCO_3$ (20 mL) was added. The aqueous layer was washed with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (30:1) to afford 0.86 g (78%) of **4.81** as a mixture of diastereomers as a yellow oil; ^{1}H NMR (500 MHz) δ 7.99-7.96 (comp, 2 H), 7.47-7.40 (comp, 10 H), 7.13-7.10 (comp, 2 H), 6.98 (br s, 1 H), 6.94-6.91

(m, 1 H), 6.90-6.87 (m, 1 H), 6.84 (d, J = 8.5 Hz, 2 H), 5.52-5.48 (m, 1 H), 5.43-5.40 (m, 1 H), 4.17-4.15 (comp, 2 H), 4.00 (comp, 3 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.26-3.22 (comp, 2 H), 2.79 (comp, 2 H), 2.67-2.65 (comp, 2 H), 2.61-2.56 (comp, 2 H), 2.49-2.47 (comp, 2 H), 1.73-1.71 (comp, 2 H), 1.50-1.45 (comp, 4 H); ^{13}C NMR (125 MHz) δ 159.2, 156.1, 152.3, 143.6, 136.3 x 2, 130.9, 130.8, 130.0, 129.3, 129.1, 128.4, 123.9, 123.8, 118.2, 116.5, 113.8, 113.2, 101.9, 72.8, 65.4, 65.3, 65.2, 55.8, 55.2, 53.4, 51.0, 40.4, 35.0, 27.3, 25.5; IR (CH_2Cl_2) 3000, 2954, 2859, 1732, 1612, 1477, 1443, 1250, 1038, 732 cm^{-1}; HRMS (CI) m/z calculated for $[C_{42}H_{49}N_2O_7S_2]^+$ (M+H), 757.2981; found, 757.2972.

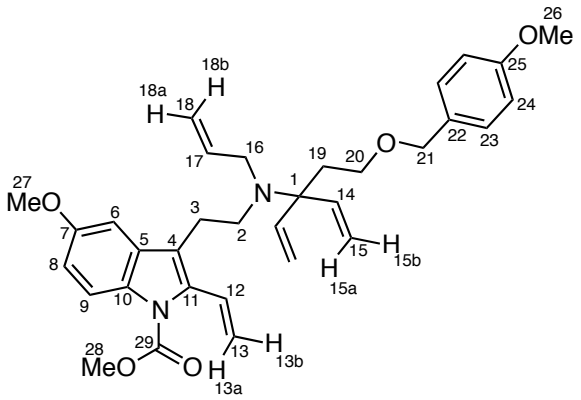
NMR Assignments. ^{1}H NMR (500 MHz) δ 7.99-7.96 (comp, 2 H, C9-H), 7.47-7.40 (comp, 10 H, C17/C18/C19-H), 7.13-7.10 (comp, 2 H, C24-H), 6.98 (br s, 1 H, C6-H), 6.94-6.91 (m, 1 H, C8-H), 6.90-6.87 (m, 1 H, C12-H), 6.84 (d, J = 8.5 Hz, 2 H, C25-H), 5.52-5.48 (m, 1 H, C13b-H), 5.43-5.40 (m, 1 H, C13a-H), 4.17-4.15 (comp, 2 H, C22-H), 4.00 (comp, 3 H, C30-H), 3.86 (s, 3 H, C28-H), 3.78 (s, 3 H, C27-H), 3.26-3.22 (comp, 2 H, C21-H), 2.79 (comp, 2 H, C3-H), 2.67-2.65 (comp, 2 H, C15-H), 2.61-2.56 (comp, 2 H, C21-H), 2.49-2.47 (comp, 2 H, C14-H), 1.73-1.71 (comp, 2 H, C15-H), 1.50-1.45 (comp, 4 H, C14/C20-H); ^{13}C NMR (125 MHz) δ 159.2 (C26), 156.1 (C7), 152.3 (C29), 143.6 (C16), 136.3 x 2 (C11), 130.9 (C5), 130.8 (C4+C19), 130.0 (C23+C10), 129.3 (C24), 129.1 (C18), 128.4 (C12), 123.9 (C17), 123.8 (C17), 118.2 (C13), 116.5 (C9), 113.8 (C25), 113.2 (C8), 101.9 (C6), 72.8 (C22), 65.4 (C21), 65.3 (C21), 65.2 (C21), 55.8 (C28), 55.2 (C27+C1), 53.4 (C30), 51.0 (C15), 40.4 (C2), 35.0 (C20), 27.3 (C14), 25.5 (C3).



Methyl-5-methoxy-3-(2-((3-(2-((4-methoxybenzyl)oxy)ethyl)penta-1,4-dien-3-yl)amino)ethyl)-2-vinyl-1*H*-indole-1-carboxylate (4.82). ALN-6-122. A solution of **4.81** (0.37 g, 0.49 mmol) and *i*Pr_2NEt (0.26 mL, 0.19 g, 1.5 mmol) in $PhCH_3$ (4.9 mL) was sparged with Ar for 4 min. The reaction was heated in the microwave oven at 150 ˚C for 3.5 h. The reaction was concentrated under reduced pressure, and the crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (2:1) to afford 0.16 g (64%) of **4.82** as a red-orange oil; ^{1}H NMR (400 MHz) δ 7.96 (d, *J* = 8.8 Hz, 1 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 7.02-6.83 (comp, 6 H), 5.73 (dd, *J* = 17.6, 11.2 Hz, 2 H), 5.49 (ddd, *J* = 19.2, 17.2, 1.6 Hz, 2 H), 5.14-5.06 (comp, 4 H), 4.32 (s, 2 H), 4.00 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.47 (t, *J* = 7.2 Hz, 2 H), 2.89 (t, *J* = 7.2 Hz, 2 H), 2.76 (t, *J* = 7.2 Hz, 2 H), 1.89 (t, *J* = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz) δ 159.0, 155.9, 152.2, 142.2, 135.8, 131.1, 130.4, 129.9, 129.1, 128.3, 118.7, 117.8, 116.3, 114.0, 113.9, 113.0, 101.7, 72.5, 66.3, 61.0, 55.5, 55.1, 53.3, 42.8, 36.5, 26.0; IR (CH_2Cl_2) 3452, 2954, 2835, 1734, 1612, 1441, 1249, 914, 745 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{30}H_{37}N_2O_5]^+$ (M+H), 505.2702; found, 505.2704.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.96 (d, *J* = 8.8 Hz, 1 H, C9-H), 7.20 (d, *J* = 8.8 Hz, 2 H, C20-H), 7.02-6.83 (comp, 6 H, C21+C6+C8+C12+C14-H), 5.73 (dd, *J* = 17.6, 11.2 Hz, 2 H), 5.49 (ddd, *J* = 19.2, 17.2, 1.6 Hz, 2 H), 5.14-5.06 (comp, 4 H),

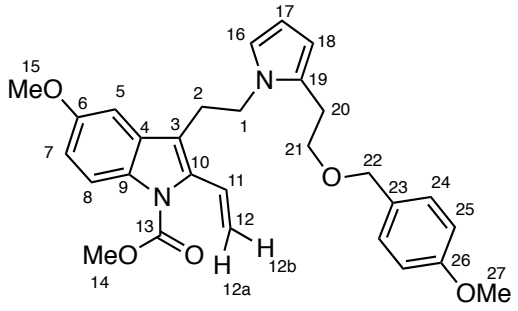
4.32 (s, 2 H, C18-H), 4.00 (s, 3 H, C23-H), 3.85 (s, 3 H, C25-H), 3.79 (s, 3 H, C26-H), 3.47 (t, *J* = 7.2 Hz, 2 H, C17-H), 2.89 (t, *J* = 7.2 Hz, 2 H, C2-H), 2.76 (t, *J* = 7.2 Hz, 2 H, C3-H), 1.89 (t, *J* = 7.2 Hz, 2 H, C16-H).



Methyl-3-(2-(allyl(3-(2-((4-methoxybenzyl)oxy)ethyl)penta-1,4-dien-3-yl)amino)ethyl)-5-methoxy-2-vinyl-1*H*-indole-1-carboxylate (4.83). ALN-6-123. K_2CO_3 (0.20 g, 1.5 mmol) was added to a solution of **4.82** (0.15 g, 0.30 mmol) and **4.16** (0.26 mL, 0.36 g, 3.0 mmol) in MeCN (15 mL) in a resealable tube. The mixture was sparged with Ar for 5 min, sealed, and placed in an oil bath preheated to 110 ˚C. The reaction was stirred for 15 h, cooled to room temperature, filtered through a celite pad eluting with CH_2Cl_2 (25 mL), and the combined filtrate and washing were concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (6:1) to afford 0.13 g (81%) of **4.83** as a yellow oil; ^{1}H NMR (400 MHz) δ 7.94 (d, *J* = 9.0 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.95 (d, *J* = 2.4 Hz, 1 H), 6.93-6.91 (m, 1 H), 6.89 (dd, *J* = 9.0, 2.4 Hz, 1 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 6.00-5.92 (m, 1 H), 5.90 (dd, *J* = 17.7, 10.7 Hz, 2 H), 5.46-5.42 (comp, 2 H), 5.25 (dd, *J* = 16.7, 2.0 Hz, 1 H), 5.19 (dd, *J* = 11.0, 1.2 Hz, 2 H), 5.11 (dd, *J* = 17.8, 1.2 Hz, 2 H), 5.09-5.07 (m, 1 H), 4.42 (s, 2 H), 3.99 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 3 H),

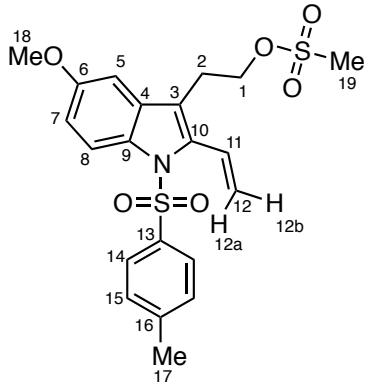
3.60 (app t, J = 7.6 Hz, 2 H), 3.28 (d, J = 6.1 Hz, 2 H), 2.86-2.82 (comp, 2 H), 2.75-2.72 (comp, 2 H), 2.08 (app t, J = 7.8 Hz, 2 H); ^{13}C NMR (125 MHz) δ 159.4, 156.3, 152.6, 141.4, 139.8, 135.8, 131.6, 130.9, 130.2, 129.5, 128.8, 119.4, 118.0, 116.6, 115.3, 114.0, 113.4, 102.1, 72.9, 67.0, 66.5, 55.9, 55.5, 54.4, 53.6, 51.5, 36.4, 27.1; IR (CH_2Cl_2) 2958, 1734, 1612, 1249, 914, 743 cm^{-1}; HRMS (CI) m/z calculated for $[C_{33}H_{41}N_2O_5]^+$ (M+H), 545.5015; found, 545.5015.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.94 (d, J = 9.0 Hz, 1 H, C9-H), 7.25 (d, J = 8.6 Hz, 2 H, C23-H), 6.95 (d, J = 2.4 Hz, 1 H, C6-H), 6.93-6.91 (m, 1 H, C12-H), 6.89 (dd, J = 9.0, 2.4 Hz, 1 H, C8-H), 6.86 (d, J = 9.0 Hz, 2 H, C24-H), 6.00-5.92 (m, 1 H, C17-H), 5.90 (dd, J = 17.7, 10.7 Hz, 2 H, C14-H), 5.46-5.42 (comp, 2 H, C13a/13b-H), 5.25 (dd, J = 16.7, 2.0 Hz, 1 H, C18b-H), 5.19 (dd, J = 11.0, 1.2 Hz, 2 H, C15b-H), 5.11 (dd, J = 17.8, 1.2 Hz, 2 H, C15a-H), 5.09-5.07 (m, 1 H, C18b-H), 4.42 (s, 2 H, C21-H), 3.99 (s, 3 H, C28-H), 3.83 (s, 3 H, C27-H), 3.79 (s, 3 H, C26-H), 3.60 (app t, J = 7.6 Hz, 2 H, C20-H), 3.28 (d, J = 6.1 Hz, 2 H, C16-H), 2.86-2.82 (comp, 2 H, C3-H), 2.75-2.72 (comp, 2 H, C2-H), 2.08 (app t, J = 7.8 Hz, 2 H, C19-H); ^{13}C NMR (125 MHz) δ 159.4 (C25), 156.3 (C7), 152.6 (C29), 141.4 (C14), 139.8 (C17), 135.8 (C11), 131.6 (C5), 130.9 (C22), 130.2 (C10), 129.5 (C23), 128.8 (C12), 119.4 (C4), 118.0 (C13), 116.6 (C9), 115.3 (C18), 114.0 (C24), 113.4 (C8), 102.1 (C6), 72.9 (C21), 67.0 (C20), 66.5 (C1), 55.9 (C27), 55.5 (C26), 54.4 (C16), 53.6 (C28), 51.5 (C2), 36.4 (C19), 27.1 (C3).



Methyl-5-methoxy-3-(2-(2-(2-((4-methoxybenzyl)oxy)ethyl)-1*H*-pyrrol-1-yl)ethyl)-2-vinyl-1*H*-indole-1-carboxylate (4.84). ALN-6-125. A solution of **4.83** (0.024 g, 0.044 mmol) in anhydrous 1,2-dichloroethane (4.4 mL) was deoxygenated 3x by removing the atmosphere under vacuum and backfilling with Ar. Grubbs second-generation catalyst (0.007 g, 0.009 mmol) was added, and the reaction was deoxygenated 2x. The reaction was heated in a microwave oven at 84 ˚C for 6 h, cooled to ambient temperature, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with Hexanes:EtOAc (6:1) to afford 0.010 g (45%) of **4.84** as a yellow oil; ^{1}H NMR (600 MHz, C_6D_6) δ 8.21 (d, *J* = 9.0 Hz, 1 H), 7.17-7.16 (comp, 2 H), 7.04 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.87 (dd, *J* = 17.7, 11.4 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 6.42 (dd, *J* = 2.7, 1.8 Hz, 1 H), 6.24 (dd, *J* = 3.4, 2.7 Hz, 1 H), 6.06 (m, 1 H), 5.25 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.97 (dd, *J* = 17.7, 1.8 Hz, 1 H), 4.26 (s, 2 H), 3.86 (t, *J* = 7.0 Hz, 2 H), 3.56 (s, 3 H), 3.50 (t, *J* = 7.0 Hz, 2 H), 3.34 (s, 3 H), 3.30 (s, 3 H), 2.91 (t, *J* = 7.0 Hz, 2 H), 2.76 (t, *J* = 7.0 Hz, 2 H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7, 157.0, 152.2, 136.8, 131.4, 131.2, 130.6, 129.8, 129.4, 129.1, 120.3, 117.9, 117.7, 117.1, 114.1, 114.0, 108.1, 107.3, 101.8, 72.8, 70.3, 55.4, 54.8, 52.8, 46.9, 27.9, 27.4; IR (CH_2Cl_2) 2955, 1734, 1612, 1441, 1330, 1249, 1123, 1033 cm^{-1}; HRMS (ESI) *m/z* calculated for $[C_{29}H_{32}N_2O_5Na]^+$ (M+Na), 511.22034; found, 511.22066.

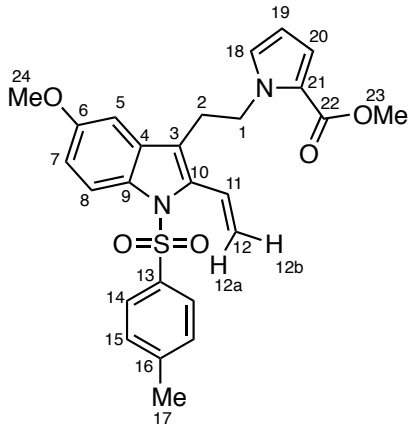
NMR Assignments. ^{1}H NMR (600 MHz, C_6D_6) δ 8.21 (d, *J* = 9.0 Hz, 1 H, C8-H), 7.17-7.16 (comp, 2 H, C24-H), 7.04 (dd, *J* = 9.0, 2.5 Hz, 1 H, C7-H), 6.87 (dd, *J* = 17.7, 11.4 Hz, 1 H, C11-H), 6.82 (d, *J* = 2.5 Hz, 1 H, C5-H), 6.79 (d, *J* = 8.7 Hz, 2 H, C25-H), 6.42 (dd, *J* = 2.7, 1.8 Hz, 1 H, C16-H), 6.24 (dd, *J* = 3.4, 2.7 Hz, 1 H, C17-H), 6.06 (m, 1 H, C18-H), 5.25 (dd, *J* = 11.4, 1.8 Hz, 1 H, C12b-H), 4.97 (dd, *J* = 17.7, 1.8 Hz, 1 H, C12a-H), 4.26 (s, 2 H, C22-H), 3.86 (t, *J* = 7.0 Hz, 2 H, C1-H), 3.56 (s, 3 H, C15-H), 3.50 (t, *J* = 7.0 Hz, 2 H, C21-H), 3.34 (s, 3 H, C14-H), 3.30 (s, 3 H, C27-H), 2.91 (t, *J* = 7.0 Hz, 2 H, C2-H), 2.76 (t, *J* = 7.0 Hz, 2 H, C20-H); ^{13}C NMR (150 MHz, C_6D_6) δ 159.7 (C26), 157.0 (C6), 152.2 (C13), 136.8 (C10), 131.4 (C4), 131.2 (C23), 130.6 (C9), 129.8 (C19), 129.4 (C24), 129.1 (C11), 120.3 (C16), 117.9 (C12), 117.7 (C3), 117.1 (C8), 114.1 (C25), 114.0 (C7), 108.1 (C17), 107.3 (C18), 101.8 (C5), 72.8 (C22), 70.3 (C21), 55.4 (C15), 54.8 (C27), 52.8 (C14), 46.9 (C1), 27.9 (C2), 27.4 (C20).



2-(5-Methoxy-1-tosyl-2-vinyl-1*H*-indol-3-yl)ethyl methanesulfonate (4.97). ALN-6-235. Methanesulfonyl chloride (0.017 mL, 0.022 g, 0.19 mmol) was added to a solution of **4.20** (0.065 g, 0.17 mmol) and NEt_3 (0.029 mL, 0.021 g, 0.21 mmol) in CH_2C_{l2} (1.7 mL) at 0 ˚C. The solution was stirred at 0 ˚C for 1 h, the cooling bath was removed, and the reaction was stirred at ambient temperature for 1.25 h. H_2O (10 mL)

was added, and the aqueous layer was washed with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford 0.079 g (>99%) of **4.97** as an off-white powder (Hexanes/EtOAc): mp 116-117 ˚C; ^{1}H NMR (400 MHz) δ 8.10 (d, *J* = 9.2 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.10 (dd, *J* = 18.0, 11.6 Hz, 1 H), 6.95 (dd, *J* = 9.0, 2.4 Hz, 1 H), 6.89 (d, *J* = 2.8 Hz, 1 H), 5.64 (dd, *J* = 11.4, 1.6 Hz, 1 H), 5.43 (dd, *J* = 18.0, 1.6 Hz, 1 H), 4.31 (t, *J* = 7.2 Hz, 2 H), 3.84 (s, 3 H), 3.15 (t, *J*= 7.2 Hz, 2 H), 2.67 (s, 3 H), 2.32 (s, 3 H); ^{13}C NMR (150 MHz) δ 156.9, 144.7, 137.3, 135.1, 131.5, 130.7, 129.6, 127.6, 126.7, 120.3, 117.0, 116.3, 114.1, 101.6, 68.6, 55.7, 37.2, 25.2, 21.5; IR (CH_2Cl_2) 2934, 1609, 1476, 1359, 1216, 1174, 665 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{21}H_{23}NO_6S_2]^{+\bullet}$ ($M^{+\bullet}$), 449.0967; found, 449.0964.

NMR Assignments. ^{1}H NMR (400 MHz) δ 8.10 (d, *J* = 9.2 Hz, 1 H, C8-H), 7.58 (d, *J* = 8.0 Hz, 2 H, C14-H), 7.14 (d, *J* = 8.0 Hz, 2 H, C15-H), 7.10 (dd, *J* = 18.0, 11.6 Hz, 1 H, C11-H), 6.95 (dd, *J* = 9.0, 2.4 Hz, 1 H, C7-H), 6.89 (d, *J* = 2.8 Hz, 1 H, C5-H), 5.64 (dd, *J* = 11.4, 1.6 Hz, 1 H, C12b-H), 5.43 (dd, *J* = 18.0, 1.6 Hz, 1 H, C12a-H), 4.31 (t, *J* = 7.2 Hz, 2 H, C1-H), 3.84 (s, 3 H, C18-H), 3.15 (t, *J*= 7.2 Hz, 2 H, C2-H), 2.67 (s, 3 H, C19-H), 2.32 (s, 3 H, C17-H); ^{13}C NMR (150 MHz) δ 156.9 (C6), 144.7 (C13), 137.3 (C10), 135.1 (C16), 131.5 (C9), 130.7 (C4), 129.6 (C15), 127.6 (C11), 126.7 (C14), 120.3 (C12), 117.0 (C3), 116.3 (C8), 114.1 (C7), 101.6 (C5), 68.6 (C1), 55.7 (C18), 37.2 (C19), 25.2 (C2), 21.5 (C17).



Methyl-1-(2-(5-methoxy-1-tosyl-2-vinyl-1*H*-indol-3-yl)ethyl)-1*H*-pyrrole-2-carboxylate (4.96). ALN-6-236. NaH (0.005 g, 0.12 mmol) was added to a solution of **4.98** (0.015 g, 0.12 mmol) in DMF (1 mL) at room temperature. The mixture was stirred for 35 min at which time **4.97** (0.030 g, 0.067 mmol) was added in one portion. The reaction was stirred for 1.5 h, placed in an oil bath preheated 70 ˚C, and stirred for 1.5 h. The reaction was removed from the oil bath, cooled to room temperature, and quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was washed with EtOAc (3 x 10 mL), and the combined organic layers were washed with H_2O (1 x 5 mL), brine (1 x 5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (200:1) to afford 0.017 g (53%) of **4.96** as a yellow oil; ^{1}H NMR (600 MHz) δ 8.45 (d, *J* = 9.1 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.19 (dd, *J* = 18.1, 11.4 Hz, 1 H), 7.09 (dd, *J* = 3.9, 1.8 Hz, 1 H), 7.02 (dd, *J* = 9.0, 2.6 Hz, 1 H), 6.52 (d, *J* = 8.1 Hz, 2 H), 5.96 (app t, *J* = 2.3 Hz, 1 H), 5.83 (dd, *J* = 3.9, 2.3 Hz, 1 H), 5.27 (dd, *J* = 11.4, 1.7 Hz, 1 H), 5.00 (dd, *J* = 17.8, 1.7 Hz, 1 H), 4.22 (app t, *J* = 7.3 Hz, 2 H), 3.58 (s, 3 H), 3.43 (s, 3 H), 2.97 (app t, *J* = 7.3 Hz, 2 H), 1.67 (s, 3 H); ^{13}C NMR (150 MHz) δ 161.7, 157.7, 144.2, 137.2, 136.2, 132.7, 131.5, 129.5, 128.9, 128.5, 127.1, 121.8, 120.2, 119.0, 118.6, 116.9, 114.7, 108.4, 102.4, 55.3, 50.6, 48.8, 27.8, 21.0; IR (CH_2Cl_2) 2950, 2836, 1704, 1609, 1475, 1438, 1173,

1155, 666 cm^{-1}; HRMS (CI) *m/z* calculated for $[C_{26}H_{26}N_2O_5S]^{+\bullet}$ ($M^{+\bullet}$), 478.1562; found, 478.1561.

NMR Assignments. Note: Proton for C5 is under solvent peak at 7.26 ppm; present in 2D spectra. ^{1}H NMR (600 MHz) δ 8.45 (d, *J* = 9.1 Hz, 1 H, C8-H), 7.64 (d, *J* = 8.4 Hz, 2 H, C14-H), 7.19 (dd, *J* = 18.1, 11.4 Hz, 1 H, C11-H), 7.09 (dd, *J* = 3.9, 1.8 Hz, 1 H, C20-H), 7.02 (dd, *J* = 9.0, 2.6 Hz, 1 H, C7-H), 6.52 (d, *J* = 8.1 Hz, 2 H, C15-H), 5.96 (app t, *J* = 2.3 Hz, 1 H, C18-H), 5.83 (dd, *J* = 3.9, 2.3 Hz, 1 H, C19-H), 5.27 (dd, *J* = 11.4, 1.7 Hz, 1 H, C12b-H), 5.00 (dd, *J* = 17.8, 1.7 Hz, 1 H, C12a-H), 4.22 (app t, *J* = 7.3 Hz, 2 H, C1-H), 3.58 (s, 3 H, C24-H), 3.43 (s, 3 H, C23-H), 2.97 (app t, *J* = 7.3 Hz, 2 H, C2-H), 1.67 (s, 3 H, C17-H); ^{13}C NMR (150 MHz) δ 161.7 (C22), 157.7 (C6), 144.2 (C13), 137.2 (C10), 136.2 (C16), 132.7 (C4), 131.5 (C9), 129.5 (C15), 128.9 (C18), 128.5 (C11), 127.1 (C14), 121.8 (C21), 120.2 (C3), 119.0 (C12), 118.6 (C20), 116.9 (C8), 114.7 (C7), 108.4 (C19), 102.4 (C5), 55.3 (C24), 50.6 (C23), 48.8 (C1), 27.8 (C2), 21.0 (C17).

Figure 5.1 View of molecule **2.88** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level

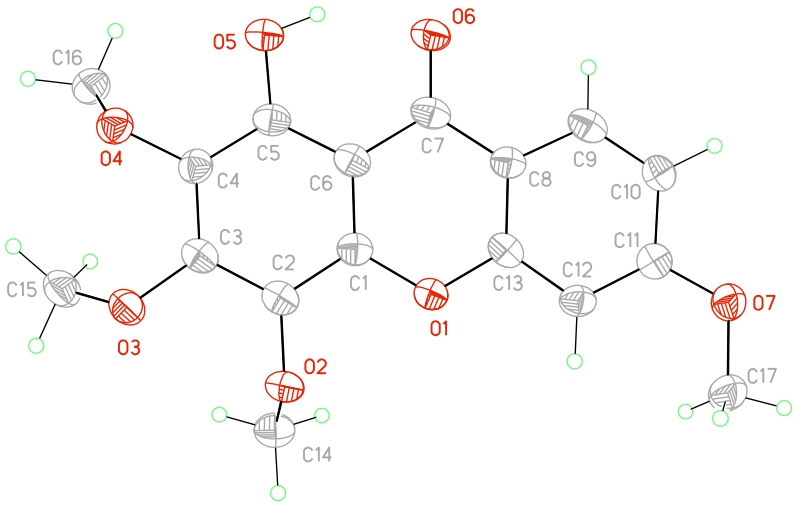
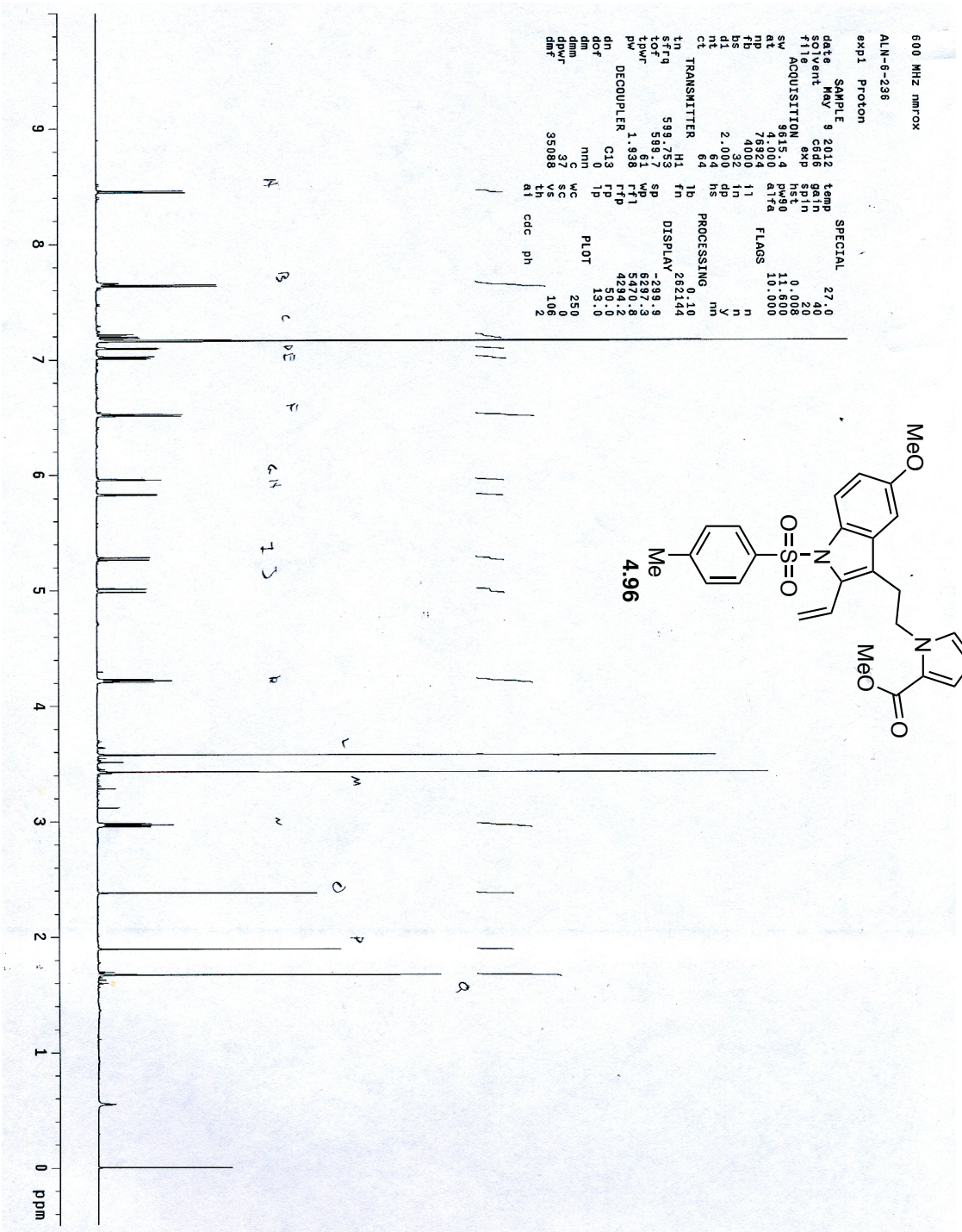
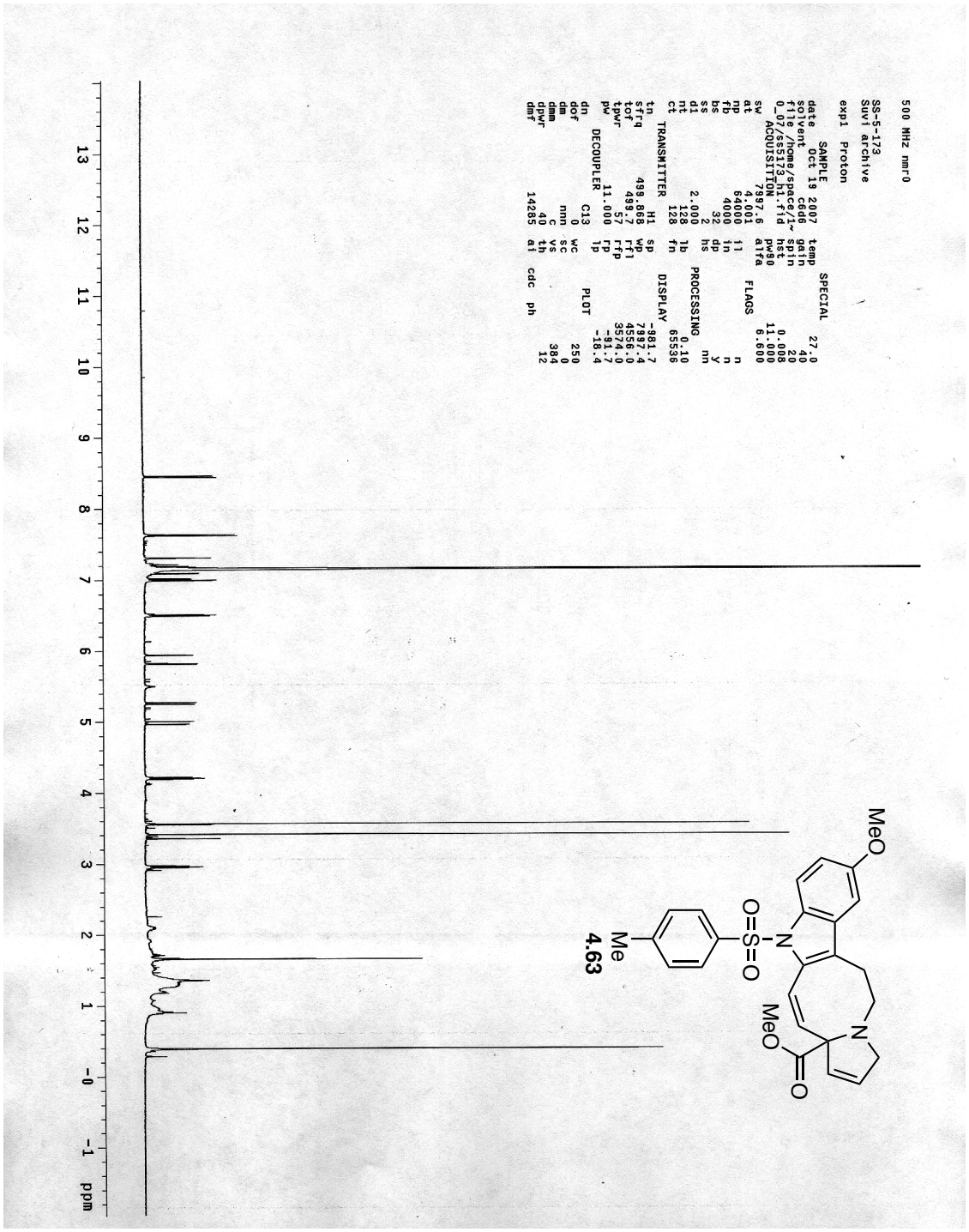


Figure 5.2 ^{1}H NMR spectrum of **4.96**



Note: peaks ‘O’ and ‘P’ are from DMF.

Figure 5.3 ^{1}H NMR spectrum of proposed tetracycle **4.63**



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